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CIS

STUDIES ON AGENT ORANGE

HEARING

BEFORE THE

SUBCOMMITTEE ON
HOSPITALS AND HEALTH CARE

OF THE

COMMITTEE ON VETERANS AFFAIRS
HOUSE OF REPRESENTATIVES

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

JULY 10, 1989

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STUDIES ON AGENT ORANGE

Monday, July 10, 1989

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, D.C.

The subcommittee met, pursuant to call, at 10 a.m., in room 334, Cannon House Office Building, Hon. G.V. (Sonny) Montgomery (chairman of the subcommittee) presiding.

Present: Representatives Montgomery, Edwards, Stenholm, Johnson, Jontz, Hammerschmidt, and Stearns.

Also present: Representative Lane Evans.

OPENING STATEMENT OF CHAIRMAN MONTGOMERY

Mr. MONTGOMERY. The subcommittee will be in order.

The purpose of our hearing this morning is to receive testimony regarding the current status of research studies concerning the possible link between exposure to Agent Orange and long-term health effects.

This is the 15th hearing on Agent Orange that this committee has held. Yet even today, the continuing controversy is the best evidence of the complexity of the topic. What our witnesses will help us do today is put into everyday language some of the scientific issues that confound the study of Agent Orange and human health effects.

Fundamental to the whole topic is the issue of exposure. We know that Agent Orange was sprayed in Vietnam and we know where it was sprayed. We know that some members of the Armed Forces served in Vietnam in areas that were sprayed. But that information is not enough.

If we want to scientifically seek a link between a disease and Agent Orange, we need to know who actually was exposed to Agent Orange and, hopefully, the level of exposure. Without such exposure information, we can only make guesses about whether a disease is related to Agent Orange.

That sounds simple, but it has perplexed many intelligent, dedicated people. I hope that today we will thoroughly explore this primary, crucial issue in order to understand the research evidence that relates to Agent Orange and human health. Without understanding the research framework, we cannot understand the findings.

I am concerned that too many times the emotion surrounding this topic is the result of apparent mismatches between hoped-for results and the actual scientific results of studies of Agent Orange.

I am concerned that attacks on the character of men and women involved in this issue have been substituted for knowledge.

Let me be clear that this committee is interested in understanding what science tells us. We will rely on the medical and scientific experts for what to do in this area. That is why the Congress created the Environmental Hazards Advisory Committee in the Department of Veterans Affairs. That is why we have relied on the technical knowledge of scientists from around the country, both independently and through the Office of Technology Assessment. We have no preconceived notion of what the results should be.

In the other body, there is legislation pending that deals with compensation for certain diseases on the basis of feared exposure to Agent Orange. We should not act until exposure is known and the link between exposure and disease is assessed. Service in Vietnam and ill-health alone are not sufficient basis for compensation.

Let me close, though, by saying if science can link exposure to Agent Orange in Vietnam and servicemen's diseases together, then compensation should be paid to these veterans that have these serious diseases.

Now, before proceeding with our witnesses, I would like to recognize John Paul Hammerschmidt, the ranking minority member on the subcommittee.

OPENING STATEMENT OF HON. JOHN PAUL HAMMERSCHMIDT

Mr. HAMMERSCHMIDT. Thank you very much, Mr. Chairman. You are to be commended for scheduling this hearing.

As you know, the subcommittee addressed the complex issue of Agent Orange last year, and we are grateful for the opportunity to receive an update on the state of the science with regard to this important matter concerning Vietnam veterans. It is an issue which is surrounded by a great deal of emotion for the thousands of veterans who believe certain disabilities are related to exposure to Agent Orange.

The committee has a strong history of support for veterans, particularly those who have suffered disabilities incurred while in service to the Nation. And for this reason, this committee continues to support the pursuit of new knowledge and research in order to reach some final conclusions about these issues.

It is important to emphasize that this committee wants to do the responsible thing with respect to benefits and services for the veterans involved. Millions and millions of dollars have been spent on many studies which have attempted to draw conclusions regarding the effect of human exposure to dioxin. More money will be spent until well-founded conclusions can be made.

Recently the Secretary of Veterans Affairs, the Honorable Edward Derwinski, decided that despite the lack of conclusive scientific evidence to date, the Department of Veterans Affairs would be willing to re-evaluate the agency's guidelines for granting service-connected disabilities found to be related to Agent Orange exposure.

It is a pleasure to receive testimony once again from the scientists we have before us today. Many of you have invested a great deal of time and effort in pursuit of answers to the perplexing

questions surrounding Agent Orange exposure. So I want to thank you for taking time to bring the subcommittee up to date on the state of the scientific information.

Thank you very much, Mr. Chairman.

Mr. MONTGOMERY. Thank you, John Paul. Don Edwards, ranking majority member.

Mr. EDWARDS. Thank you, Mr. Chairman. I want to join with the others in thanking the chairman and commending him for holding these hearings and for continuing to pursue this important problem with the tenacity that he has. Mr. Chairman, I especially want to welcome Oliver Meadows, who I believe was staff director when I first came on this committee 26 years ago. He is a great friend, and friend of the veterans.

Mr. MONTGOMERY. Thank you for recognizing Oliver Meadows. I am glad to see Charlie Stenholm, Tim Johnson, and Lane Evans here this morning. The Chair would like to point out to our witnesses, I tried to keep my statement under 5 minutes. We can get more into it if members have certain questions they would like to ask, and if any of the panel groups would like to make any comments, the Chair will recognize you if you want to make any other comments.

We are sorry that a representative from the New Jersey Agent Orange Commission couldn't be here today. They were invited, and it was not possible for them to make it. But, without objection, their testimony will be included in the record.

[The statement of New Jersey Agent Orange Commission appears on p. 39.]

Mr. MONTGOMERY. If there is no objection, we will call on Ms. Hellen Gelband, who is a senior associate for the Office of Technology Assessment, which is an arm of the Congress.

STATEMENT OF HELLEN GELBAND, SENIOR ASSOCIATE, OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS, ACCOMPANIED BY ROGER HERDMAN, M.D., ASSISTANT DIRECTOR FOR HEALTH AND LIFE SCIENCES, OFFICE OF TECHNOLOGY ASSESSMENT

Ms. GELBAND. Thank you for the opportunity to testify at this hearing. I am accompanied by Dr. Roger Herdman, Assistant Director for Health and Life Sciences at the Office of Technology Assessment.

I have a brief opening statement. Just over a year ago I testified before this subcommittee on what was known about exposure to Agent Orange in Vietnam. Summarizing briefly, men whose jobs regularly involved handling herbicides—Air Force Ranch Hands and chemical corpsmen, mainly—had exposures high enough to result in persistent elevated body burdens of dioxin. Other men had occasional direct exposures from spraying around bases with backpack or truck-mounted sprayers. Most ground troops, however, probably had relatively little exposure. When Congress mandated an Agent Orange study in 1979, the biggest design problem for the study was thought to be identifying enough men who had been in Vietnam and were unexposed to serve as a comparison group. Only after several years of painstaking research in the military records,

and finally measurements of blood dioxin levels in veterans, did an altered picture emerge. During the last year, research has tended to confirm the validity of blood dioxin levels as a marker for heavy exposure in the past. No information has come to light that would alter the conclusion of a year ago.

Claims have been made by the American Legion that their own study, published in December of last year, does provide evidence to the contrary. OTA reviewed that study in January 1989. We found that major flaws in the design preclude the conclusions drawn from it linking exposure to Agent Orange with subsequent health effects.

In the past year, new information on exposure using blood dioxin analysis has also come from the Ranch Hand Study, and from preliminary results of a National Institute for Occupational Safety and Health study of former production workers exposed to dioxin. Also, a report was published recently updating mortality data for the population exposed around Seveso, Italy, a site of heavy dioxin contamination. Studies still in progress include the Ranch Hand Study, the Selected Cancers Study being conducted by the Centers for Disease Control, the Department of Veterans Affairs Proportionate Mortality Study, and continuing studies by the New Jersey Agent Orange Commission.

I would be happy to answer questions or go into detail on any of these issues. Thank you.

Mr. MONTGOMERY. Thank you very much for your interesting statements. Certainly we will have some more comments from you.

[The prepared statement of Hellen Gelband appears on p. 44.]

Mr. MONTGOMERY. Dr. Houk, Director for the Center for Environmental Health and Injury Control, Centers for Disease Control, in Atlanta, GA is our next witness.

STATEMENT OF VERNON N. HOUK, M.D., DIRECTOR, CENTER FOR ENVIRONMENTAL HEALTH AND INJURY CONTROL, CENTERS FOR DISEASE CONTROL

Dr. HOUK. Thank you, Mr. Chairman.

First, Dr. Mason asked me to apologize for him. He wanted to be here today, but he got back from Africa late last night and was unable to make it.

Since his and my testimony in June of 1988, nothing has changed to alter the conclusions that we brought before the committee. In fact, the data that have become available since then have reinforced those conclusions. I have prepared extensive testimony which I will not even briefly review.

Mr. MONTGOMERY. Without objection, the full testimony of all the witnesses will be put in the record.

Dr. HOUK. Since I prepared the testimony, the Half-Life Study has been published, and I will submit that for the record. Members of your staff already have a copy of it.

[See p. 84.]

Dr. HOUK. Two things that have happened that are of major import. One, last month in San Antonio, TX, Dr. Mocarelli from Italy reported the first 11 years experience from Seveso, Italy. In the Seveso incident, there are about 700 people who had dioxin

levels at the time of that incident up to 5,000 times background levels. We found individuals with 27,000 parts per trillion. Those people have absolutely nothing that can be determined to be of any clinical significance other than chloracne. Over 600,000 laboratory tests have been done in this population over the ensuing years, and there are no abnormalities other than the chloracne.

The Columbia University Legionnaire Study is very similar, Mr. Chairman, to the questionnaire part of the Vietnam Experience Study that we presented last year. The people who thought they were exposed and served in Vietnam reported higher incidences of almost all medical conditions. However, as you well know, when we validated those, by conducting examination on over 4,000 veterans we could not verify the abnormalities that they reported.

In addition, as we discussed extensively last time, we could not validate the exposure by TCDD levels in very few of these people, even though they reported heavy exposure.

Thank you.

Mr. MONTGOMERY. Thank you, Doctor.

[The prepared statement of Vernon N. Houk, M.D. appears on p. 59.]

Mr. MONTGOMERY. Next will be Dr. Yanders, Chairman of the Scientific Council, and Oliver Meadows, Chairman of the Veterans' Advisory Committee on Environmental Hazards.

The Chair will recognize Mr. Meadows first.

STATEMENTS OF ARMON YANDERS, PH. D., CHAIRMAN, SCIENTIFIC COUNSEL; AND OLIVER E. MEADOWS, CHAIRMAN, VETERANS' ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS

STATEMENT OF OLIVER E. MEADOWS

Mr. MEADOWS. As you indicated earlier, the Advisory Committee on Environmental Hazards was created by the Congress to give advice to the Veterans' Administration, and its organization was set out in the legislation. It has 4 lay members and an 11-member scientific council that consists of experts on radiation, as well as dioxin.

We operate out in the open, and we pass on our recommendations to this committee, to the Senate committee, and to the Secretary of Veterans Affairs.

One of our principal functions is to review scientific literature and give the Secretary our opinion as to the validity or usefulness of this scientific literature. We have reviewed hundreds of papers, and in this regard I might point out that a paper is not necessarily a study and a study is not necessarily a paper. There are a few scientific studies. There are a good many surveys, there are lots of comments on comments and lots of debate, and there are a lot of articles that appear in the scientific publications that we look at and try to give the Secretary the benefit of our opinions.

At the present time we are involved, as the law requires, in advising the Secretary on the promulgation of new regulations that are the result of a recent decision in the Federal courts that is altering the regulatory standard for evaluating the scientific literature and we are just into that process now and will be involved in

it until about the end of September, going through the usual phase of regulation, public comment and so forth.

As a layman, there are four of us lay people on this committee, along with the scientific members. If someone asks me, what do you think are the strongest indicators that you have heard anything about? I would have to point to the Ranch-Hand Study and the blood assay program, and I was impressed by the Australian study, the study the Australian Government did of its around 7,000 participants in the Vietnam war.

We have already commented on the various studies, and I am sure Dr. Yanders will give you the substance of the comments on any of the studies that you might care to ask him about. We have transmitted our findings to you already through the staff.

Mr. MONTGOMERY. What are your findings?

Mr. MEADOWS. I will let Dr. Yanders, Chairman of our Scientific Council, respond to that. And I will at this point introduce Dr. Yanders.

[The prepared statement of Mr. Meadows and Dr. Armon F. Yanders appears on p. 88.]

STATEMENT OF ARMON YANDERS

Dr. YANDERS. Mr. Chairman, members of the committee, I want to thank you for the opportunity to appear here today. My prepared statement describes the composition of the Scientific Council of the Veterans' Advisory Committee on Environmental Hazards and the way in which the committee evaluates the pertinent literature which Mr. Meadows touched on.

With your permission, I would like to omit much of that and concentrate on the committee's response to the recent court decision that the VA and committee applied the wrong standard in attempting to determine whether it would be appropriate for VA to award compensation for claims based upon exposure to Agent Orange.

The committee concurred with the determination of VA that sound, scientific and medical evidence did not establish a cause-and-effect relationship between dioxin exposure and porphyria cutanea tarda, soft tissue sarcoma, or any other disease except chloracne. The court stated a requirement for a cause-and-effect relationship was stricter than had been intended by Congress. The court found the Congress intended VA to make a finding of whether or not there existed a significant statistical association between dioxin exposure and a subsequently appearing disease.

The Secretary asked Mr. Meadows to convene a meeting of the Advisory Committee to assist in the development of criteria by which it may be determined whether there exists a significant statistical association between two separately occurring events, in other words, between exposure and the onset of disease.

Mr. Meadows consulted with me, and we determined that it was important to respond to the Secretary's request just as soon as possible. Accordingly, a special panel of the committee was convened, and it met on June 26 to consider a proposal designed to be consistent with the court's order.

It is my understanding that the comments of the committee were considered by VA and that a proposed rule will be published soon

for public comment. When the comment period ends the panel will be reconvened to consider the comments received by VA, whatever comments other committee members may have made, and the response of the VA to those comments. We will then offer our views and recommendations to VA, and VA will then publish its final rule.

In November, the full committee will meet and will assess the scientific literature in light of the standard articulated in the regulation.

Mr. Chairman, I know you have asked for the assessment of the committee of the relevant scientific literature at this time. I think you will understand if we respectfully decline to provide you that assessment today because of the pending change in the appropriate standard for judging the literature.

I would hesitate to speculate on what the committee's position will be after it applies the standard or what recommendations it may make to VA in light of the standard. I do want to assure you, however, that the committee will enter into this process with an open mind and will take very seriously the charge to reconsider the scientific literature and to make whatever recommendations we then believe are appropriate.

Thank you very much.

Mr. MONTGOMERY. Thank you, Doctor.

The Chair recognizes Dr. Stellman, co-author of the American Legion-Columbia University Study on Vietnam Veterans.

STATEMENT OF JEANNE MAGER STELLMAN, PH. D, CO-AUTHOR, THE AMERICAN LEGION-COLUMBIA UNIVERSITY STUDY OF VIETNAM VETERANS

Dr. STELLMAN. Thank you, Mr. Chairman.

I appreciate the opportunity to come especially in front of this committee which has received an onslaught of criticism about our study. I know that this is all in the record, but I feel it incumbent to inform you that my husband cannot be here, he is Assistant Commissioner of Health for New York City and is busy in the city and could not make it. We have submitted written testimony.

We carried out, as you know, a cross-sectional study of a random sample of Vietnam veterans, two-fifths of whom served in Southeast Asia, and all of whom were members of the American Legion. The study was supported by the American Legion and carried out by us at Columbia University and the American Cancer Society.

You have heard informal testimony today and informal critiques that our study is seriously flawed. This is a particularly surprising announcement for several reasons, and I am going to take a couple of minutes to tell you why.

One of the major flaws perceived in this committee is use of our combat scale. I would like to call the attention of this committee to the recently released, Research Triangle Institute Report, which showed not only that our 8-point combat scale was valid, but in fact one only needed five items in order to converge.

In a recent public forum, the director of that $10 million congressional study stated that he had never seen two studies conceived of

and carried out so differently converge so exactly on the same findings.

I think although this hearing, which is directing its attention to Agent Orange, and is focused purely on Agent Orange, and especially only on dioxin, overlooks the multivariate nature of combat experience and the Vietnam era experience which must take combat and herbicide exposure and a multitude of other exposures in those jungles in Vietnam into account. An "experience" study, a study that only concentrates on the mere presence or absence in an area of the world without regard to the major variables of interest is going to fail to observe most findings.

We found this very, very strongly in our study, and we are very gratified to see that the Research Triangle Report considers this kind of classification is the over-arching variable of interest, that unless one takes combat into account and unless one classifies by exposure, you will simply dilute away all of your effects.

It is also surprising to hear the Office of Technology Assessment say that all of our findings are so flawed that they must be disregarded, in the words of John Gibbons.

One of the other major alleged flaws, in addition to this combat scale—which we didn't invent, which has been in use since 1979, has a reliability of 98 out of a scale of 100 and was found to be completely reliable with regard to the records that were investigated by RTI—in addition, we are accused of misclassification. This is a tremendously interesting criticism because the results of misclassification of exposure in a cross-sectional study can only do one thing: It can only make effects which are there disappear. One can't create effects by misclassifying veterans, and I will just take one minute to explain this in layman's language.

If you have people who are exposed, and in fact who consider themselves exposed or are found to be exposed, and in fact they are not exposed, then you get a lower rate in the exposed group than you would have if they were in fact and they were truly exposed. Similarly, if your control group contains people who aren't controls but are exposed, then they are going to get a higher rate. So misclassification tends to do what we call as biased towards the null, that is to make effects that may be there disappear. In a cross-sectional study, one cannot create effects by misclassification.

We have heard our exposure referred to as a perceived self-exposure. In 1986, we published results of an earlier study presented by us. We consider veterans' self reports of exposure to be highly unreliable. We specifically did not use them. This is in complete agreement with the CDC's earlier study on birth defects, where they find a relationship between self-perceived exposure and outcome but not between actual exposure. Our classification system, in fact, is one that is very similar to the one we think is being used as the creation of the exposure index in the so-called validation study of the CDC.

Finally, I find it absolutely astounding that a system which is based on more than 12,000 actual—more than 20,000 actual spray records of 12 million gallons and some—well, in this particular study we actually didn't use the troop movement tapes but we now have troop movement tapes, we find it incredible a study that is based on the same exact kind of data the National Academy of Sci-

ences use in their massive study, and which in fact led to stopping the spraying by the United States, is being called into question by people who fail to ask, why are we lending such credibility to the Ranch Hand Study which takes the total gallonage of herbicide that was dumped on Vietnam and divide it by the number of people present in any job category? Does that mean if someone went a whole exposure, your exposure went up; and if three extra guys came on in your job classification your exposure went down? I am not saying ours is a perfect measure.

On the other hand, to fail to point out the inconsistencies of standards that are being used is, I think, to fail to do your job in terms of assessment. But the greatest failure is to fail to talk about where the data all converge, and that, I understand, is the purpose of your meeting today. In fact, if one took the time to actually look at the data instead of going through all this methodological hand-waving criticism that seems to go on, one would see that there is a great convergence of data in the VES study, RTI study and our study on psychological well-being—depression and anxiety, post-traumatic stress disorder, and other psychological problems; physical health—history of hypertension, chloracne, other skin problems, liver conditions other than cirrhosis and hepatitis, fertility problems, possible clinical left ventricular hypertrophy, possible chest X-ray abnormalities, hearing loss, peripheral neuropathy, evidence of past hepatitis; laboratory findings: abnormal gamma-glutamyl transferase, fasting glucose, thyroid-stimulating hormone, occult stool blood; reproductive health—low sperm count and abnormal morphology; increased birth defects—nervous system anomalies, musculoskeletal deformities, anomalies of the integument, and hydrocephalus; increased miscarriage rate.

We took the opportunity of plotting the CDC data versus ours and find not only do they have the same dose of response effects but a greater dose response effect in miscarriages.

The Air Force study's interim report (February 1988) showed statistically significant differences between Ranch Hand personnel and controls in 6 of 11 targeted clinical areas: increased cancer, increased birth defects, psychological changes, hepatotoxicity, cardiovascular changes and endocrine changes.

I want to also state that although there have been some negative studies, there is a growing body of literature on the effect of other components of the herbicides, not simply TCD, and cancers in agriculture and forestry workers both in Sweden, Denmark, Italy, and in the United States studies carried out by the National Cancer Institute and negative studies from the Veterans' Administration have no credible—purport to show no relationship of Agent Orange exposure, have no credible evidence that a sufficient latency period has gone by, and there are too few subjects by which we can have meaningful analyses.

Mr. MONTGOMERY. Would the doctor mind wrapping it up? I have been very generous with time.

Dr. STELLMAN. I will finish in 30 seconds.

I wish to say we have taken some time to answer some of the critiques presented to you, and I want to call your attention to a letter we wrote to you and members of this committee in 1986 before we knew of the presence of additional troop movement data

in which we outlined carefully the kinds of studies one could do from the knowledge of the gallonage used and which the National Academy of Sciences has used so successfully, and I would refer you back to that.

Thank you very much.

Mr. MONTGOMERY. Thank you, Doctor.

[The prepared statement of Jeanne Mager Stellman appears on p. 90.]

Mr. MONTGOMERY. Our last witness this morning—and to my colleagues this is the last panel, so we should have enough time to get into this subject as we should—Col. William Wolfe, principal investigator of the Ranch Hand Study, Department of the Air Force.

STATEMENT OF COL. WILLIAM H. WOLFE, M.D., PRINCIPAL INVESTIGATOR, RANCH HAND STUDY, DEPARTMENT OF THE AIR FORCE

Colonel WOLFE. Thank you.

I am accompanied today by Gen. Mike Torma and Dr. Joel Michalek, one of the principal investigators on our study.

I appreciate the opportunity to provide the committee with an update on the Air Force health study. We have been actively involved in this issue since October of 1978 and have had several reports published. Reports on the results of the 1982 and 1985 physical examinations were released in 1984 and October of 1987, and those reports, in general, found the health of the exposed men, or men we assumed were exposed, was equivalent to that of the comparison group.

The 1987 report found lifetime systemic cancers appeared to be higher in Ranch Hand enlisted fliers as contrasted to their comparisons.

After continuing verification of the data, correction of coding errors, and gathering of additional medical records, no significant group differences in lifetime systemic cancer were found on reanalysis of that corrected data. Similarly, the 1987 cardiovascular evaluation showed when heart disease of all types was considered, Ranch Hands were found to have more disease than the comparisons.

Re-analysis of these data after continuing evaluation of reported conditions and additional medical record review, revealed that significant group differences are no longer present in verified heart disease.

Data from the 1987 physical examinations are currently being analyzed, and a report will be released in early 1990.

In addition to the morbidity analyses, periodic evaluation of the death experience of the Ranch Hand and comparison groups have been conducted and reported. Those reports have repeatedly demonstrated similar death experience in the two groups with no apparent effects from herbicide exposure. The latest analysis was released in April of this year. This most recent evaluation differs from previous statistical contrasts in that the mortality experience of the entire comparison population, in excess of 19,000 men, has been used as the standard for assessing Ranch Hand mortality. The indirectly standardized Ranch Hand mortality rate for all causes of

death is 2.5 deaths per thousand person years. And the corresponding rate for the entire comparison population is also 2.5, giving an overall relative risk, assessing Ranch Hand mortality with comparisons, of one.

Digestive system deaths are more frequent in the Ranch Hands relative to the comparison population. However, five of these six deaths were attributable to alcohol consumption.

We have also observed a statistically significant increasing trend in death rates among Ranch Hand flying officers since 1983. In previous reports, this subgroup of officers had lower mortality than their comparisons, though this difference was not statistically significant. At the present time, the two groups appear to have equivalent mortality. Whether this represents an ongoing trend or just a correction or balancing out of the statistics, we are not sure, but we are very carefully following this group on an annual basis to assess their mortality.

There has been much controversy concerning the relationship between herbicide exposure and birth defects in children. Initial evaluation of fertility and reproductive outcomes found there was significant disparity between the groups for reported birth defects, birth defects reported by the parents.

We initially over-interpreted that data and incorrectly concluded that group differences were confined to minor skin conditions at the base-line report in 1984. That base-line finding of overall-group differences in reported birth defects is being reinvestigated with medical record verification of the health status on all 6,723 children fathered by study participants. Medical records were obtained for all but 89 of those children. This rate of missing records is exceptionally low and will strengthen the statistical analysis of that data. A report on the results of this reanalyzed confirmed data will be ready for submission to our Advisory Committee next year.

Our initial study protocol included an estimated exposure index that reflected our best calculation of the effective number of gallons of herbicide which each individual could have been exposed to during his service in Vietnam. Individual exposure measurements could not be made, and while the method used to establish the exposure index was state of the art, variation due to individual work habits and circumstances could not be avoided.

By mid-1986, strong evidence was demonstrated by the Centers for Disease Control and other institutions that dioxin levels could be measured in blood, as well as fat tissue. Serum has been collected and stored from 19,999 study participants. To date, we have the assays on 1,005 of those men in hand from the CDC. The remaining specimens should be completed by the end of this year, and we will then be able to reanalyze the 1987 physical examination data in light of that data.

It appears very clear to us, even from the first look at that data, that the men who served in Vietnam and handled herbicide in bulk quantities on a repetitive basis do in fact carry elevated body burdens of dioxin to this day, and other men, general infantry ground troops, C–130 air crew and support personnel, have levels at or below normal levels.

We appreciate the efforts of this committee to help us include these assays in our work, and we will give you those results when they become available.

Thank you very much.

[The prepared statement of Colonel Wolfe appears on p. 114.]

Mr. MONTGOMERY. Thank you very much.

That concludes our panelists, and the Chair would like to recognize Cliff Stearns of Florida.

Mr. STEARNS. Thank you, Mr. Chairman. I just ask unanimous consent to place my opening comments into the record.

Mr. MONTGOMERY. Without objection.

Mr. STEARNS. I want to thank you sincerely for allowing the full committee membership to come to this hearing to listen. Back in my district, a lot of folks have been asking me questions. Now I have an opportunity to get some answers. Thank you very much.

Mr. MONTGOMERY. I hope we can answer some of those questions.

The Chair will implement, as we always do, the 5-minute rule, then we will go around to members and come back again for the questions.

The Chair, without objection, will recognize staff members to ask some technical questions.

Dr. Houk, there has been criticism about the recommendation of CDC not to proceed with the Agent Orange exposure study. Please tell us why you decided not to proceed.

Dr. HOUK. Mr. Chairman, the exposure of Vietnam veterans to Agent Orange has been one of the most perplexing issues I have dealt with in my public career. I spent between 10 and 25 percent of my own time since 1980 on this issue.

As part of our superfund activities in the Missouri dioxin spill, there was an individual who was exposed in the Bubbling Springs Riding Arena in 1971 and had no other exposure since 1971. We measured dioxin in that individual's fat in 1983 at 750 parts per trillion. This gave me the impetus to ask my laboratory if they could devise a technique to measure it in blood since we could not use fat. People who had been exposed significantly would have elevated body burdens.

Working with the Army, the environmental support group and Mr. Christian in designing the Agent Orange study, we elected to use Army veterans who served from 1968 to 1969 in the III Corps area, and that is because III Corps was the area most heavily sprayed, and 1968–1969 was the period where the most spraying occurred.

Between 1963 and 1968, with Mr. Christian and our group, we developed information on 14,483 veterans, of which 9,727 met study eligibility criteria. We chose the veterans for several different reasons from their military records. There were five parts of the military record that we looked at. One, the veteran was within, or his company was within 2 kilometers up to 6 days after spraying as documented in the herbicide tapes, aerial spraying, or fixed spraying known for Agent Orange.

Because the half-life in soil is about 5 years, we also looked at a score based upon if the veteran was within 2 kilometers at any time he served in Vietnam. We also looked at the sprays of unknown agents. There were known Agent Orange sprays and there

was a group of sprays for which the agent was unknown. We looked at those, both 2 kilometers in 6 days or 2 kilometers at any time.

We then looked at whether they served in five specific zones in III Corps, which got 70 percent of the sprays. We then asked the veteran—there was a questionnaire—whether he had been present during the spraying, whether he handled herbicides or whether he had herbicides on his skin or clothes. We then asked the question, did he go, walk through or clear vegetation of a previous area? These are seven exposure indexes——

Mr. MONTGOMERY. I don't have but 5 minutes.

Was any political pressure put on you to stop this study by any group?

Dr. HOUK. By no means, sir.

Mr. MONTGOMERY. No political pressure?

Dr. HOUK. No political pressure on any of the results or to stop it.

Mr. MONTGOMERY. Do any other panel members want to comment on political pressure that they know about, comment on what the doctor just said?

Mr. MEADOWS. I would only want to say, Mr. Chairman, we have never had any sort of pressure or suggestions applied on either side of the issue. We have been left free to render our own independent judgment.

Colonel WOLFE. On the part of the Air Force, we have been uninfluenced, unpressured. The modifications to our protocol and examinations have been based solely on the comments on our own working group and of our Advisory Committee.

Mr. MONTGOMERY. Let me get a clarification. You mentioned at the end of your remarks—my time is up, so give me a brief answer—that there were levels of dioxin by the blood tests. What did you mean by that? Were other groups showing that too, or just the Ranch Hand group?

Colonel WOLFE. The State of New Jersey, I believe, has done a study of a small number of men; they found several of their people who did have elevated levels, those that had elevated levels were either members of our Ranch Hand group or chemical sprayers. But, in general, our ground enlisted, the crew chiefs, the men who maintained the aircraft and spray systems, had elevated levels——

Mr. MONTGOMERY. For the record, how about certain diseases? Did they have a higher ratio than those who lived in Saigon?

Colonel WOLFE. We have not analyzed the results in light of their levels yet. We are still continuing with the testing, but we will have those results available in about a year-and-a-half. Six months more for the testing and a year for the data analysis and report writing.

Mr. MONTGOMERY. I am confused. What are you waiting on?

Colonel WOLFE. We are waiting to complete the dioxin testing. We are approximately 50 percent complete. We have almost 2,000 men who have given us blood and we have 1,000 results in hand. CDC will finish the remainder by the end of this year. We will then use those serum levels, as our exposure index, and will re-analyze the results of the 1987 physical examination in that light.

Mr. MONTGOMERY. I guess where I am coming from, we keep having to wait a year, a year from now, 2 years from now, and people on both sides of the issue would like to get some information.

Colonel WOLFE. Yes, sir.

Mr. MONTGOMERY. Now you are telling me another year-and-a-half.

Colonel WOLFE. In our initial efforts, we did the best we could with our calculated exposure index. But 2 years ago or 3 years ago now, when this assay became available, that basically made a whole new ball game for us. It will really allow us to very accurately determine exposure. We will no longer be forced to make assumptions about how clean or dirty people worked and how much they really were exposed. That will really clarify a lot of——

Mr. MONTGOMERY. The Chair recognizes Mr. Hammerschmidt.

Mr. HAMMERSCHMIDT. Thank you, Mr. Chairman.

Colonel, let me just pursue your testing a little further. I am assuming, correct me if I am wrong, it is the general consensus of scientists on this panel here the most reliable and valid measure of exposure is the blood test developed by the Centers for Disease Control. Is that correct?

Colonel WOLFE. Yes, sir, that is correct.

Mr. HAMMERSCHMIDT. Let me pursue Chairman Montgomery's line of questioning a little bit.

Dr. STELLMAN. Excuse me, sir. That is not correct, that is not the universal opinion of all the scientists on this panel.

Mr. HAMMERSCHMIDT. We have one dissenting view of Dr. Stellman, let the record show.

Let me pursue the chairman's line of questioning. Dr. Michael Gochfeld made this statement last year about the CDC Agent Orange exposure study, and he made this in an editorial, and I will quote: "The Centers for Disease Control has, however, declined to perform these congressionally mandated studies, arguing since exposure cannot be well documented, the study was not feasible."

Could you comment on his quote, Dr. Houk?

Dr. HOUK. Yes, I can, and I think that is still correct. Dr. Gochfeld also told this committee in June of 1988, "You have heard Dr. Mason say the results of the New Jersey and CDC study agreed, and I think that is very important. They are remarkably close, almost too close if you are going to predict it."

He further stated, "The Agent Orange validation study is primarily an exposure study, and it establishes a methodology for using the blood tests as a surrogate or an indicator of past exposure."

Yet 6 months later, he strongly criticized the results of our study and argued for use of an unvalidated exposure method. This is no different, Mr. Hammerschmidt, than we see in the general population when people think they are exposed. As you know in your own State, the PCBs around Jacksonville, we cannot find exposure in those people. They have normal blood levels and at the background level.

If people are occupationally exposed, we can have elevated levels. There are people in the occupational studies whose exposure stopped 30 years ago that have up to 1,200 parts per trillion in

their blood. The normal background level is up to about 10 to 15 parts per trillion. This is the way of getting at a measure of exposure by doing this.

Dr. Stellman compared the results of the CDC validation study with her study. I would point out those are the self-reported results of veterans and not validated results.

Mr. HAMMERSCHMIDT. Thank you.

Dr. Stellman, let me give you an opportunity to describe the method you used to assess the health status of veterans.

Dr. STELLMAN. Well, first, in our particular study we used a survey method. Our study is not the end all and be all, as no single study is, and I don't think that whether or not a questionnaire for a set of studies reflects yes or no is particularly relevant to the overall question of how does one evaluate exposure 20 years post-Houk.

It is true some people heavily exposed to a substance, to a dioxin-contaminated substance, will still continue to have dioxin in their blood stream. There is a great deal we do not know, however, about the sequestering of dioxin in the tissues. We do know now fairly well there is about a 7-year half-life. That means every 7 years the concentration will diminish by half.

There is nothing wrong with using a blood test to confirm that someone was exposed. The great fallacy, in my opinion, is to use a blood test to say that nobody else was exposed.

I hear over and over and over again the use of the term "unvalidated" to describe taking the spraying tape data from the HERBS tape assembled by the National Academy of Sciences and supplemented by the environmental support group, reporting 20,000 missions, some 12 million gallons which were not sprayed all over Vietnam but sprayed in discrete locations, and it is continually called unreliable and unvalidated to compare the people who were in the sprayed areas to the many, many, many people who were in the unsprayed areas. It is not a technique we have made up, it is a standard technique of epidemiology and one the National Academy found quite adequate.

Mr. HAMMERSCHMIDT. As I understand, your survey was done through the mail; is that correct?

Dr. STELLMAN. Yes.

Mr. HAMMERSCHMIDT. Did you actually see any of the exposed veterans in person or take any blood or do any physical test?

Dr. STELLMAN. We did a study the way scientists all over this country do cross-sectional studies.

Mr. HAMMERSCHMIDT. On your own study, it was done by mail.

Dr. STELLMAN. Our study was done by mail, yes. Our study was confirmed down to a tenth of the decimal point by the larger personal interview and questionnaire validation method of the research triangle. If you are interested in the methods we used, I suggest you get the people in to discuss that.

Mr. HAMMERSCHMIDT. To further pursue that, you actually didn't see or physically examine any veteran, is that correct?

Dr. STELLMAN. No. We never claimed to.

Mr. HAMMERSCHMIDT. I realize that. I just wanted to get it in the record.

Thank you very much.

Dr. STELLMAN. Our $83,000 study was done by mail.

Mr. HAMMERSCHMIDT. What was the price?

Dr. STELLMAN. It was $83,000 as compared to $63 million.

Mr. HAMMERSCHMIDT. Thank you very much.

Mr. MONTGOMERY. Don Edwards.

Mr. EDWARDS. Thank you very much, Mr. Chairman.

Mr. Meadows, what do you think of this disagreement? Who do you think is right?

Mr. MEADOWS. Our Scientific Council routinely looked at this so-called American Legion study, before the recent court decision, and I hope you will appreciate we are rather guarded now because we will have to re-evaluate that study in light of the new standard now being developed. I am going to remind you, the answer which we have already made and transmitted to this committee was before the court decision.

The impression I have is that these self-reporting studies, and Dr. Yanders can be more specific, these self-reporting studies are notoriously unreliable, and also, as I recáll, there was a serious problem in the lack of response, the number, the percentage of responders, so serious it was probably jeopardized. The general conclusion of our scientific panel, I believe I can say, was it was not a reliable, useful study.

Dr. STELLMAN. May I respond to that? Our response rate in fact was higher than the CDC's validation response rate, number one. Our response rate was higher than the CDC validation study response, number one; and, number two, the CDC study on VES compared their telephone interview with their examination, and they found that the only discordance between the examination and the telephone was that men had under-reported their skin effects.

So I am sitting here listening as if these things are not writen down on a piece of paper. We are not the only people to have done a study like this, and our data is completely concordant with other people's data. One can always—this is exactly what the tobacco industry has done for years every time someone has claimed tobacco smoke causes cancer or some other illness. They raise these smoke screens and fail to look at the consistency and uniformity of responses. We found a dose response relationship. We compared veterans in three combat levels to veterans—we had four ways of cross-classifying and cross-stratifying, and that is a way of doing internal comparisons.

I am a professor of public health at Columbia. I have taken time off of my Guggenheim Fellowship to come here. My husband is in charge of all the vital statistics in New York City and was Associate Director of a million-person study at the American Cancer society, we know how to compare 2,000 veterans in one group to 2,000 in another.

Mr. EDWARDS. Thank you.

My last question, Mr. Chairman, is for any member of the panel to respond to briefly. I went on a committee-sponsored visit to Vietnam in December, 1983 to see what kind of statistics we could find collected by the Vietnamese. We had a great deal of difficulty because recordkeeping there is very rudimentary. At that time, there was only one study that had been made, and it was not taken seriously because most people thought that the people who were

making the study were predisposed to come to a particular conclusion.

It just seems to me that there were a lot of Vietnamese in those forests in the foliage that was defoliated with Agent Orange. What kind of studies have been made? Did any of you go over to Vietnam and check with the Vietnamese?

Dr. HOUK. Mr. Edwards, when I was the chairman of the Science Panel of the Agent Orange Working Group, we looked at this issue in very great detail. Dr. Woodward, one of the grand old masters who was employed at the Veterans' Administration, had been there and advised us. The records situation in Vietnam was such that the conclusion was that no valid study could be done.

Mr. EDWARDS. Your organization didn't send anybody over there?

Dr. HOUK. No, sir, but Dr. Woodward had been there.

Mr. EDWARDS. Thank you, Mr. Chairman.

Mr. MONTGOMERY. Don Edwards and I have both been over there a number of times. I don't have any problems trying to find out what happened on the Vietnamese. As you said, though, no records were kept. I'm not sure what information could be gathered. It would be worth looking into like we have looked into the Australian report, too.

Thank you. The Chair would recognize those who are on the subcommittee and then would recognize those who are from the full committee and the way you came into the meeting.

Charlie Stenholm from Texas.

Mr. STENHOLM. Thank you, Mr. Chairman.

Dr. Houk, your statement that this has been one of the most perplexing problems that you have faced in your career, I think, could be safely said by everyone at the table. I think there is a reason for that because it has been the same problem that we have had in almost every other area of scientific pursuit of cause-and-effect of cancers or other various diseases.

I think part of that comes from a fairly accepted standard that 99 percent of the known carcinogens in the world occur naturally. Therefore, it is difficult to prove beyond a shadow of a doubt what causes what in any of us, whether we were in Vietnam or whether we were involved in agriculture. The latter is in an area where I am considerably more familiar with a large number of studies attempting to link various products used in the production of food with cancer and its causes and effects.

I know the frustration that all of us feel because certainly no one currently involved in agriculture would want to continue to use something if it was proven beyond a shadow of a doubt that it was going to cause something harmful to the population as a whole.

And that is why I am extremely interested in the process of the study. The Ranch Hand Study, I think, should begin to give us some evidence as to whether there is any linkage between dioxin and disease.

Did I understand, Dr. Stellman, that you disagree with that basic possibility?

Dr. STELLMAN. Yes. The National Academy of Sciences National Research Counsel reviewed that protocol when it was first done. They calculated a simple epidemiology one power statistic. It

doesn't have sufficient power to detect an elevated cancer rate even over 20 years.

All of this—listen, as difficult as it may be for a layperson to understand, cancer is a statistically rare disease. It occurs in a living population at a rate for all cancers of about 100 to 100,000. We are not talking about all cancers.

In particular, the ones we are talking about in the selected cancer study, for example, are relatively rare cancers so that rate is considerably less than 100 per 100,000. You have 1,267 men, so that is one, what, one one-hundredth, no, it is one-tenth of—I am sorry. I cannot do this in the halls of Congress too quickly. It is one-hundredth, approximately, of 100,000.

At most you are going to expect every year one, two cancers for overall cancer. This should be in your records some place. I am not making this up. I don't come to Washington that often. That study has never from its initial conception, it's initial design, have the statistical power to detect excess cancer.

Every year we go through this exercise of listening to a Ranch Hand Study report. The only time they all seem to agree is when they all want to get together and target in on anybody else who does a study. That seems to be the only time we get a unanimity and a surge of energy here.

Mr. STENHOLM. Dr. Stellman, I was not questioning that. My question was whether the blood dioxin study is a reasonable way to proceed to determine cause and effect?

Dr. STELLMAN. I am not suggesting our study is perfect.

Mr. STENHOLM. Are you saying the blood dioxin test is irrelevant?

Dr. STELLMAN. No. The first time the Air Force published blood assays I was heartened because I didn't think they would find anything at that point in time. The description in the New Jersey study, the study were incorrect. Those were ground men in the New Jersey Point Man Study. That and the CDC study showing evidence of, still having TCCDs some 20 years post-exposure, even though it is not clear who was in the study, I think, to me is confirmation of what we know from the military records and the spraying records that a large number of people were in areas that were sprayed.

I think there are many biochemical questions. I am a chemist and a toxicologist. I am not a biochemist. I think you need to get before you a panel of people who will comment on the fatty metabolism of agents such as TCCD, their sequestering, what is the effect.

If one of the effects of TCCD is wasting, losing weight, what is the effect of someone suffering the effects on their blood? If someone ends up losing a lot of weight, does that cause them to have a rapid loss of TCCD?

We have a few studies that now give us a pretty good idea that we have a 7 year half-life, but we have no idea of all the rest of the dynamics. I think it is an interesting and an important approach. It is hardly the *sine qua non*, the only approach.

It is unscientific to say there is only one approach to a problem like this. If we cannot figure it out on this approach, we throw out 12 million gallons of spray records because this one method that

hasn't even been fully scientifically investigated by credible scientists in the open literature is the only way to do it.

When the CDC undertook its serum validation test, there wasn't a published study on the relationship between blood and fat. If you read their paper published in 1988, they refer to the Point Man Study and their own study published 3 years afterwards as the rationale for why they could do that study. That is not how you do science.

You need to have many different groups looking at it. If you are interested in the TCCD, you should get somebody, some biochemists to do the analysis of how it is going on. I am not saying the CDC lab isn't good. They are an excellent lab, and they can do it as long as there is an agreed upon protocol.

Mr. STENHOLM. Mr. Chairman, my time has expired. I think I heard a few mis-statements of fact in the dissertation. I want to check the record and ask Dr. Stellman to clarify some of the statements she made concerning some of the studies.

Dr. HOUK. Mr. Chairman, the cancer issue that Mr. Stenholm brought up is an important issue. We are not relying on Ranch Hand. We recognized this when we did the Vietnam veterans' studies. There would not be sufficient numbers of cancers in that population to arrive at any decision.

We, therefore, are coins in the Selected Cancer Study, which is looking at Hodgkin's disease, non-Hodgkin's lymphoma, and carcinoma of the liver. These are the cancers that were predicted in animal studies.

Those results will be available to this committee in a final report in March of 1990. The study has very good power for the soft tissue sarcoma and the lymphomas and less power for the nasal pharyngeal frinio carcinoma. We will have to wait until that study is completed before we can get sufficient numbers out of this.

This is a population cancer registry based study which is going to be important for this committee's deliberations on these issues.

Mr. MONTGOMERY. Colonel Wolfe.

Colonel WOLFE. Just a couple of comments, if I may. The Air Force has very clearly recognized our power limitations on the identification of specific types of cancers. That is why our reports focus on skin cancers as a group and systemic cancers as a group.

Also, Dr. Stellman's comments on the New Jersey Point-Man Study, they called it "point man". In fact, in their published article, they do refer to the fact that quite a few of their individuals were members of Ranch Hand.

Mr. MONTGOMERY. The Chair would like to recognize Lane Evans, the chairman of the Subcommittee on Oversight and Investigations.

Mr. EVANS. Thank you, Mr. Chairman. I wanted to thank you for inviting me to the hearing today.

Last year's hearing therefore acknowledged the data from the 1984 Ranch Hands Report and all subsequent reports would have to be re-assessed in light of a new exposure test based on serum dioxin levels. The Air Force said it was too early to make statements until that data was re-assessed.

Why did you claim at the National Environmental Health Conference that there appeared to be no significant health problems in the Ranch Handers?

Colonel WOLFE. On balance, based on the overall group analyses, Ranch Handers versus comparisons, looking for consistency and across general physical areas, that was our conclusion at that point.

Mr. EVANS. This conclusion, this cannot be based on the new exposure index; is that correct?

Colonel WOLFE. That is correct.

Mr. EVANS. Why would you make such optimistic statements given limitations of existing exposure index?

Colonel WOLFE. We tried to reach a conclusion based on the data we have, caveated on the fact that we are waiting the outcome of the more definitive essay.

Mr. EVANS. That is a pretty big caveat, isn't it?

Colonel WOLFE. It is a caveat that needs to be made. We very clearly laid that out so that it is very clear to the readers of our reports.

Mr. EVANS. I am not sure that is coming across in the press. I think you have been over-optimistic in general statements. You have also told the press that skin cancers were the only significant increase in the Ranch Hand group. The UPI article quotes you as saying skin cancer is something we want to keep looking at. But the big problem is taking into account sun exposure.

Isn't it true in your testimony last May you confirmed the excess in skin cancers in Ranch Handers could not be explained by overexposure to the sun?

Colonel WOLFE. We are trying to refine that.

Mr. EVANS. What did you say to the Senate Veterans' Affairs Committee last year, that it couldn't be explained as a result of overexposure to the sun?

Colonel WOLFE. As of that time, as we were able to measure sun exposure.

Mr. EVANS. What is the explanation for making this statement to the press?

Colonel WOLFE. We have now come upon a data based from the Air Force, data based on geographic locations as to the annual number of days of sun in each, in Denver, CO, in Minneapolis, MN, in Atlanta, GA, in Dallas, TX, in San Diego, CA. In those previous analyses we used a very crude measure, if you will, of sun exposure. It was based on northern latitudes versus southern latitudes, a dichotomous choice.

Mr. EVANS. Point me what report that is in.

Colonel WOLFE. In the October 1987 report, the morbidity report.

We have since discovered it is possible to use this additional data base to come up with a more exact measure of sun exposure. We don't know what effect that will have, but it will be a more precise way to assess sun exposure.

Mr. EVANS. I am not sure I quite understand what you are saying. You are saying you may have a way of taking into account the impact of sun exposure, but you don't have any definitive data on that as of yet?

Colonel WOLFE. We are just developing the use of that data.

Mr. EVANS. Why the statement to the press and the American public that, "The biggest problem is taking into account sun exposure"?

Colonel WOLFE. As far as looking at whether the skin cancer is related or not to herbicide exposure relies on several things. Sun exposure is a contributing factor to skin cancer in general.

The other factor that will help us clarify, get a better understanding of that finding will be the serum dioxin results so we can, in fact, determine whether that is just a group difference or whether it may be related to exposure.

Mr. EVANS. You verified, other scientists have verified in the past the apparent doubling of birth defects in Ranch Hand children; is that correct?

Colonel WOLFE. As reported by parents.

Mr. EVANS. The final report is pending?

Colonel WOLFE. We have gathered medical records on those children.

Mr. EVANS. Why 5 years?

Colonel WOLFE. It is an extremely labor intensive, laborious process to locate medical records on 7,000 children through the age of 18. Many studies rely on birth defects as listed on birth certificates, in which are anything short of disastrous birth defects are often missed. We are looking at the health status of these children through the age of 18. It is very labor intensive and very time consuming to gather that many records on that many people.

Mr. EVANS. Mr. Chairman, I would like to come back when I get an opportunity to do so.

Mr. MONTGOMERY. Thank you, Lane.

Any member of the panel, now is the time to raise your hand. The Chair will recognize you to comment on what any of the panelists have said.

Dr. Houk.

Dr. HOUK. Mr. Chairman, we would like to make clear that the Columbia American Legion Study authored by the Stellmans and others is consistent with the interview portion of the Vietnam Experience Study. Many findings were reported by the veterans. When we brought a random sample of over 4,000 veterans to Albuquerque, we could not validate their abnormalities. This is consistent with what we see in the civilian population.

Also, Dr. Stellman obviously chooses to ignore or hasn't read much of the work on the blood levels of dioxin, which is fairly extensive. The half-life with first order kinetics is 7 years. That would be two-and-a-half half lives after people left Vietnam. We have demonstrated high levels in the Ranch Handers, we have demonstrated high levels in occupationally exposed people, in exposed people in Missouri. It is a very good surrogate for exposure. If the dioxin levels are at background levels, they, in all likelihood, have not been significantly exposed to Agent Orange.

Mr. MONTGOMERY. Thank you.

Cliff Stearns?

Mr. STEARNS. Thank you, Mr. Chairman. We have heard the comments by Dr. Stellman and Dr. Houk and, I think, Colonel Wolfe. I would like to get comments also from Ms. Gelband and Dr. Yanders, if they would, give them an opportunity to speak here.

Please comment on the methods talked about and their reliability, and particularly comment on what the other witnesses have talked about.

Ms. GELBAND. I would be happy to start. Thank you.

There are a number of things that have been brought up. I think it might be worthwhile to concentrate on a couple of points.

In Dr. Stellman's testimony, she talked about other studies of dioxin-exposed and phenoxyherbicide-exposed individuals. We should separate the question of whether phenoxyherbicides cause disease from the question of whether Vietnam veterans in general were significantly exposed to Agent Orange in Vietnam.

I am not going to talk right now about whether dioxin or phenoxyherbicides cause disease, but concentrate on whether people other than Ranch Handers and other individuals who handled herbicides directly were significantly exposed.

Much of the criticism of the American Legion study has been, as Dr. Stellman pointed out, about the exposure assessment. But the criticism hasn't been of the Ranch Hand HERBS tapes, as far as I know.

I think what Dr. Stellman referred to as the "NAS Study" was simply the transcription of Ranch Hand spray mission grid coordinates onto a computer tape that could be used for further research. I don't know exactly who did the transcription, but the Academy did look at the tape and verified that it was a very accurate transcription of the Air Force spray records. No one is questioning that.

We probably have a pretty good idea of where Agent Orange was sprayed. That is not the aspect of the American Legion Study exposure estimate that has been questioned.

The other part of the exposure problem is determining where people were in relation to this spraying. And that is the question that CDC worked on for so long, that the Agent Orange Working Group struggled with, and that OTA reviewed time and again when various methods were proposed.

As far as we can tell, based on the 1986 paper by the Stellmans and the later papers published in December of last year, the method that they used to locate people used on self reports, that is, people were given a list of places and a map, and reported where they were on these dates in which they were in Vietnam, and then matching up those reports with the HERBS tapes.

CDC tried a more sophisticated approach than that, using military records of troop movements, and found you could have a reasonable idea of where people were in relation to spraying.

What they then found, though, was that people just weren't directly exposed to spraying very much, and they really weren't often in areas that received spray right after spraying.

Another aspect of the American Legion Study exposure assessment is that they used a distance of 15 kilometers from a spray path as in the exposure zone, although the exposure zone would be lower at 15 kilometers than it would at 1 kilometer for the spray line. What is known about spraying of the type done by operation Ranch Hand is that there is very little, if any, spray drifting more than 2 kilometers from a spray path.

So classifying anyone as "exposed" who was between 2 kilometers and 15 kilometers may in fact represent saying that people were exposed when they had no chance to be exposed.

Most of the people in the study had those kinds of exposures—several kilometers from the spray paths. These are the issues with exposure that we are critical of and concerned about.

Dr. STELLMAN. May I correct a factual error here? I am sorry, but we have repeatedly had this. This is not a matter of difference in opinion. This is a matter of understanding what an exponential decay equation means.

The number 15 that OTA keeps referring to is the upper limit at which we simply stopped calculating the exposure. We didn't calculate the 5, 10 or 15. We did a continuous exposure. We stopped at 15. Otherwise, the computer would go on all night providing no additional data.

The report is written by someone who does not understand a first order exponential decay. I will be happy to explain it to you. I think it will take more than 5 minutes that one is allowed.

It is an inaccurate description of how one calculates exposure. I think OTA ought——

Mr. STEARNS. I was going to ask Dr. Yanders if he would like to respond. That is my last question.

Dr. YANDERS. I will make a very brief comment. I don't want to continue the analysis of the Columbia University study because when our committee examined that, we decided it was so seriously methodologically flawed that it did not appear to be useful for the deliberations of the committee or for the Veterans' Administration.

It seems to me I would like to focus on something which was touched on by Dr. Houk earlier. That is a report given by Dr. Mocarelli at the Environmental Health Conference in San Antonio, TX, a couple of weeks ago. This was a report of the exceedingly high levels of dioxin in the blood which had been archived for many years, and in some cases, there was a 5,000 times background level in the blood in people who did not even exhibit chloracne at the time nor have they since.

I think what we are beginning to learn from this study, the Ranch Hand Study, is that so far we see no ill-effects with people with any relatively high levels. I think this is beginning to show that although it may be very toxic and harmful for many experimental animals, in man the hazards of dioxin are over-rated.

Mr. STEARNS. Thank you, Mr. Chairman.

Mr. MONTGOMERY. We will start another round. The Chair will ask the panel members, especially Dr. Houk and Colonel Wolfe, of those individuals in Vietnam that you have examined and had high levels of dioxin, can you relate at this time, or have you seen any cancer diseases that could be related to high levels of dioxin from your studies?

Colonel WOLFE. Mr. Chairman we have not looked at the serum levels themselves at this time. However, it is clear from our data, as included in our formal testimony. There is a chart in the back of that material that clearly shows a graduated levels of exposure with the officers being on the low end of the scale, the enlisted flyers being moderate and the ground support personnel, the enlisted ground personnel being the highest.

Without using the specific and individual dioxin levels, the best surrogate for exposure we have is occupation. Occupation has been a co-variable in all of our analyses. In general, we have not seen any increases in cancer in one of our occupational groups over another.

Initially we did have an increase in the systemic cancers in that enlisted flying group. However, when we were able to obtain additional medical reports, additional clarifying information so that we could better validate those diagnoses, that finding was no longer present.

Mr. MONTGOMERY. In layman's language, the cancer rate of these thousand individuals who really handle this Agent Orange is no higher than any other group in America is what I am trying to find out.

Colonel WOLFE. Other than skin cancer, we do have the skin cancer finding, as Mr. Evans mentioned. As far as systemic cancers go, we are not finding any increases in that area.

Mr. MONTGOMERY. Dr. Houk?

Dr. HOUK. As I said, Mr. Chairman, the cancer issue as it relates to Vietnam service must await the completion of the Selected Cancer Study which will be done and presented to you in March of next year on those selected cancers.

The power is really quite good. However, there is no evidence of occupational exposure of the few incidents that have been studied, and NIOSH is doing a mortality study that will be out very soon.

In Seveso, Italy, which we keep talking about because it is so important, there were 700 people who have up to 5,000 times background level; 192 of those people were children at the time of exposure, 1 to about 6 years of age.

This is now the twelfth year since Seveso, Italy. Based on everything we know about cancer models in animals, at least in the young, we should begin seeing something of an increase about this year. None of these children in Seveso, Italy, with these high levels have any malignancy. There is no excess of malignancy in the Seveso, Italy population, despite what was reported very recently regarding which we sent you—I think—a letter.

Equally important, other than cancer, is that there were no birth defects. These are people with tremendously high exposure, both men and women. There were no birth defects. There is no increase in spontaneous abortion, no increase in low birth weight, no neurologic abnormalities.

The only abnormality was chloracne. There are no differences in the abnormalities between the exposed and the unexposed group from another part of Italy.

Mr. MONTGOMERY. Dr. Stellman, we are not trying to pick on you, but it seems no one on this panel except you agree with the study that you have done for the American Legion.

Dr. STELLMAN. I can put together a panel that would agree. It was a peer reviewed study. It was published. I suggest if you want to have a less biased committee, you ought to start off with the people from Research Triangle and the people from the New York State Psychiatric Institute.

If the chairman wishes, I will be happy to give you a selection of names that you can go and investigate the privately sponsored

American Legion study in a way that some of these other much more expensive publicly funded studies have not been investigated.

I would like to say we have just listened to this discussion on Seveso, Italy. There were 211 families in the immediate zone and 3,000 people in Zone B. Many of them were children. If you have virtually no statistical information among the 1,200 adult Ranch Hands, you have still less among the Seveso, Italy population.

Mr. MONTGOMERY. Let me mention one thing, Doctor. This committee was the one that influenced taking this Agent Orange study several years ago away from the Veterans' Administration that was going to do the study; and the American Legion, the people who paid for your study, recommended that is a great idea. Let's move it down to CDC. Now they have changed their positions.

Dr. STELLMAN. Mr. Chairman, let me say I have been the thesis advisor and the colleague and a mentor for many people in the CDC. My husband directs a CDC contract now. We have a great deal of respect for the CDC, and we have excellent working relationships with many branches and have been advisors to many branches of the CDC.

I have never understood why this is happening. I have always been very surprised. We have been astounded at the response to what we consider to be a relatively small study for some of the studies that we have done, this kind of concerted attack on this. I just find it unbelievable that we can hear statements saying, well, we have examined these records, and we don't think they are any good.

Mr. Chairman, there is not one single detailed paper talking about how the mathematics was done, and what was done, what are the exposure distributions. We have just gotten 40 tapes with hundreds of thousands of data points which the CDC somehow reduced to a two digit number and never described in any detail how they did it.

We are asking for a fair day in court.

Mr. MONTGOMERY. Thank you.

The Chair will recognize Mr. Hammerschmidt. I am a little hurt you didn't send me a questionnaire. I would go to Vietnam eight different times during the war, and I was exposed to Agent Orange. But I cannot remember the dates. I don't know how these young soldiers could exactly know what time and how close they were to it.

I am not trying to hurt your study, but you cannot poll people and come up with something that is factual and you can make a statement——

Dr. STELLMAN. Mr. Chairman, first of all, had we had this data that we have now gotten, we would have been extremely happy to actually use military units. But we did a very thorough, we believe, statistical analysis of the responses and the patterns of response to those questions.

The fact is that Agent Orange, herbicides were not sprayed all over Vietnam. They were sprayed in discrete locations. Those people who could not fill out their maps were removed from the study. I am sorry that you didn't get a questionnaire. You were obviously not in the random sample. We have been accused of lying

that we had not randomly sampled. Next time maybe your number will come up.

Mr. MONTGOMERY. Thank you.

Let me recognize the General.

General TORMA. Mr. Montgomery, the Air Force Medical Services wants to do the responsive thing on behalf of its veterans constituency. We recognize the tremendous obligation to those who have and those who continue to serve.

Put very simply, my role on the Air Force Surgeon General's staff as a newcomer to this issue is to ensure we discharge that obligation responsibly and toward that end, I bring to that task practice a scientific eye, and I can assure you a dispassionate attitude in the sense I have not directly participated in any studies alluded to today.

With that as a preamble, if I may, I would like to address a few points. You may recall in testimony last year General Sloan tried to give the committee a concept of what "parts per trillion" really mean. He likened it to taking a second off your watch and comparing it to 32,000 years. That is one part per trillion.

If you can imagine the vagaries of spray in whatever gallons and the small amount of contaminant, the dioxin we are talking about settled out through clouds, foliage, applied unevenly to battle dress, applied unevenly to skin, washed off quickly in some cases, washed off not so quickly in others, you can understand the difficulties of estimates and indices.

In that regard, in science there is nothing better than a peak. An awful lot of logical finesses doesn't always turn out to be true. We are, with the help of our colleagues, applying final, real objective measurement to all the parameters which at this point have been subjected to the kinds of estimates you are talking about with regards to accuracy and bias.

Let me say this, I assure you that the Air Force study has been conducted with the finest possible objectivity we can bring to bear on the subject. Because of the vagaries of analysis in things like estimates, we believe our statistical approach, particularly with the validation by way of serum studies and tissue where it is available, is the appropriate way to go.

In fact, we feel that to assign decimal point accuracy to a computer construct with the vagaries of drift and everything else that I have just alluded to, flies in the face of very basic statistical principles.

In terms of Mr. Evans' comments, let me return to the basal cells and to the studies you have alluded to. I'd like to remind the panel the Air Force's study is a 20-year longitudinal study. It is appropriate, therefore, to provide intermediate reports based on the best evidence at the time. That is in fact what our investigators have done.

In terms of basal cells, there is an interesting phenomena. The Ranch Hands do have more reported basal cells than their constituent coherts. By Dr. Stellman's concept, we would not have found that true, because we would not have had a large enough group to do that.

What we are finding is that distribution of basal cells is distributed across the level of Ranch Handers. That is to say the pilots

exhibited basal cells, the people in the backs of the aircraft have exhibited basal cells, and those of the ground crew have exhibited basal cell carcinoma.

Now, we know in a preliminary sort of way that there is a general increasing exposure to the herbicide in measures that have been reported thus far at least. Those that are the ground handlers have the highest aggregate numbers, and that is part of the report submitted today. Those in the back of the aircraft have a somewhat lesser aggregate number but still higher than those in the front end of the aircraft.

One would assume if we were seeing a dose-response relationship of any sort that there would be a progression of findings of basal cell carcinoma so that the ground handlers would have the largest proportion of those. To this point at least that has not been the case.

We are faced with a perplexing finding, a very real one in our Ranch Hand group, which to this point we cannot explain, certainly not on the basis of dose response to Agent Orange. Therefore, we continue to look at other variables like the sun factor for possible answers. The jury isn't in on that, and we continue to investigate it.

Mr. Chairman, thank you for your time.

Mr. MONTGOMERY. Dr. Houk?

Dr. HOUK. Mr. Chairman, we are having some disagreements about exposure and the physical health effects. Dr. Stellman refers to the RTI study and their studies being concurrent. They are very much the same in the Vietnam experience study. They are all concordant on the psychological issues. They are different on the physical health issues.

Using a strict criteria, we reported to this committee last year 2.2 percent of the Vietnam veterans experience an episode of posttraumatic stress disorder within a month of examination or up to 20 years after leaving Vietnam. That is an issue that I don't think the difference of who was exposed and not exposed and who were should not cloud that issue because this is a very significant finding for the Vietnam veteran, the psychological problems, not many, but a few of them are experiencing.

Mr. MONTGOMERY. Mr. Hammerschmidt?

Mr. HAMMERSCHMIDT. Well, let me just discuss the chemical side of this for a minute and get comments from the panel.

Some people have suggested that dioxin may not be a health risk at all, but that 2,4,2-D, another component of Agent Orange, may be. Is it safe to assume the level of dioxin measured by the blood test would also be a valid and reliable proxy measure for other components of Agent Orange?

Before you comment on that, if it would be a good proxy, then any health effects found to result from known high exposures would be useful knowledge even if a link between dioxin and disease are not known. Do you agree with that?

Dr. HOUK. Agent Orange is a 50–50 mixture of 2,4,5-T and 2,4,2-D. The 2,4,5-T is contaminated with dioxins. Any use of dioxin as a surrogate for exposure to Agent 0range is also a surrogate for exposure to 2,4,2-D. We do not know what all the exposures were in Vietnam. They are not only chemical exposures, but we know the

veterans returning from Vietnam have a higher incidence of Hepatitis-B. We expect that because that is higher in that part of the country.

I think what we have to realize if we find an increase in certain of the malignancies it is going to be due to service in Vietnam. You cannot say it is due to exposure to anything other than the entire exposure to the service in Vietnam.

Mr. HAMMERSCHMIDT. Let me pursue that a little bit further. I know Ms. Gelband wanted to comment on the other subject. Let me ask you something, Ms. Gelband, from your statement.

On Page 5 of your testimony, you state it is uncertain whether blood dioxin determinations in people who already have cancer would be valid. Would you please explain that statement further?

Ms. GELBAND. Well, actually, Dr. Stellman mentioned this. All of the validation so far looking at past exposure and current levels of dioxin has been in relatively healthy people. It is possible that at a time when somebody has advanced cancer and their body metabolism has changed, their physiology has changed in response to the cancer, you might not find the relationship you would in healthy people.

I imagine as the test gets used more, we will find out more about that. Right now, you couldn't assume if you didn't find it, it meant no exposure, although if you did find high levels, it probably would mean significant past exposure. I don't think we are ready to make that first jump just yet.

Mr. HAMMERSCHMIDT. Dr. Stellman?

Dr. STELLMAN. I want to agree very much with the general's comments that one cannot use these exposure indexes as they have been used down to a decimal point level. We never used to a decimal point level. Perhaps that is part of Mr. Chairman's misunderstanding.

All we did was to classify people into not, low exposure, modest, and high exposure. I absolutely agree with him that one cannot just go to a decimal point. That is exactly what is wrong with the serum validation study in which these data were reduced to a two digit number to the tenth decimal place and then compared to laboratory values which have a much higher precision.

Despite the crudity of using that kind of exposure, they had a correlation of about 40 percent. If anything, it vindicates the use of these records. I absolutely agree with the general. I think the power calculations really dealt with systemic cancer and did not address the skin cancer.

The reason you are getting a different dose response could be an ozone co-factor from flying up there as opposed to being on the ground.

Mr. HAMMERSCHMIDT. Dr. Stellman, Mr. Dickrin, at the meeting of the Veterans Advisory Committee on the Health Effects of Herbicide stated the study of which you are co-principal investigator was not designed to determine the relationship between herbicides and cancer; is that correct?

Dr. STELLMAN. The American Cancer Society has done two extremely definitive studies. I think you read on your little cigarette panels warnings based solely on several reports and to a large extent on the American Cancer Society questionnaires on cancer.

We didn't put cancer into our study because it was too soon. The pre-test began in 1984. Secondly, we didn't have the money to do a cancer study.

We have heard all these discussions about power. Power is your ability to detect an effect. To detect a cancer effect among American Legionnaires, we would have had to do a substantially larger study.

When we began the study, I was very skeptical that Agent 0range had in fact caused something. We set up an American Legion study that included post-traumatic stress, social and behavioral effects. We included herbicide questions because, of course, that is a major question, and we included the utilization of the Veterans' Administration in the study. We did this for two reasons. There are other important things.

Also, I was absolutely not certain that we would see anything. Despite the aura that is given off here, we did not go in there with an axe to grind. We didn't think it was worth spending the money and the time on increasing the number of people at such an early date post-exposure because we didn't think there would be any cancers.

Mr. HAMMERSCHMIDT. Your survey did not reflect the cancer?

Dr. STELLMAN. It was not designed to.

Mr. MONTGOMERY. Mr. Evans?

Mr. EVANS. Dr. Stellman, did you have $80,000 to do the study?

Dr. STELLMAN. I think the Legion budgeted $100,000. I don't remember. They came in at $83,000.

Mr. EVANS. Suppose I gave you $63 million to study this problem, would you have in that study been so strict to restrict the study only to Army soldiers who served in Vietnam? Would you have been so restricted to restrict that study of Army veterans to only those who were E–1 through E–5, that served 180 days or more, but not over one tour in Vietnam?

Dr. STELLMAN. No, I would never have instituted any of those restrictions on the study population. For your information, Mr. Evans, my husband and I serve as exposure consultants to the Agent 0range Veteran Payment Program. In that regard, we have had the chance to look at the military history of some 20,000 claimants now.

I have permission of the court to speak of these results. This may be off a little bit because the computer went down before I came to Washington, but the majority, and I cannot give you the exact figure, the majority of people who have claimed under the Agent 0range Veterans Payment Program would have been excluded from the CDC study because they shifted units and they served more than 1 year. I don't know about the ranks. They don't have that information computerized.

Mr. EVANS. I have given you $63,000,000. Would you think you'd come before this committee and tell me you couldn't find enough people to sample basically out of 2.4 million veterans who served in Vietnam?

Dr. STELLMAN. No. The thing I object to is this whole idea there is only one way to do a study, you know, science is a careful building up like building blocks. I object to the idea of some kind of platonic ideal saying this is the ultimate study.

You can take any problem in the world and methodize it to death by setting up all the different criteria. The late statistician Jerry Cornfield used to call that a council of perfection.

I think there are so many interesting—it is kind of a dispassionate academic term to use, for important areas that could be examined in a whole series of small, smaller exciting, innovative and open studies that say, okay, there is something wrong. Our exposure technique isn't perfect. We had a little computer and a HERBS tape to go with it. We have taken 40 more reels of tapes on our computer and can classify many, many more people.

You don't need $63 million. You need a positive attitude to say we have 12 million gallons. We know they were dropped. We know there were a lot of troops that served in Cam Ranh Bay and other areas that there was no spraying. We can compare Cam Ranh Bay to Ben Hoa and come up with a study of two groups, one with a much lower exposure than the other.

We keep hearing this allusion to occupational studies. I have never seen such a collection of data on environmental uses of herbicides and environmental contaminants and the locations of people in any occupational study, including TCDD, including asbestos as we have languishing in front of us.

Mr. EVANS. Let me thank you because I thought I heard you mention at one point that you had gathered or analyzed 1,000 data points, and that reminded me of something President Bush said about 1,000 points of light.

We want to thank you for lending us thousands more data points of light, you might say. The Legion did support the transference of the study from the VA to the CDC, but I think funded this program along with Columbia University because they feel the CDC totally with the VA in $63 million worth of funding has not done the job. We appreciate it.

I might also note I understand the New Jersey Agent Orange Commission would have at least supported some of your conclusions. They were not able to be with us here today.

If I have the time, Mr. Chairman, can I continue for a few more questions?

Mr. MONTGOMERY. Sure.

Mr. EVANS. All right. Colonel, I would like to go back to you for a minute. I would like to jump from cancer problems to other problems relating to the mortality study that I think indicated there is an excess among the Vietnam veteran group in violent deaths. Is that correct?

Colonel WOLFE. Accidental deaths in the first few years after they returned.

Mr. EVANS. Accidental violent deaths?

Colonel WOLFE. Automobile accidents primarily, airplane accidents. There were five gentlemen killed in a single aircraft accident.

Mr. EVANS. Your mortality report didn't show an excess in what you might call violent death? I am not sure how that is defined. You were talking about accidents?

Colonel WOLFE. We were talking about external causes, that is the way they are defined in the medical records coding. They include accidental deaths, non-disease deaths.

Mr. EVANS. Would they include violent——

Colonel WOLFE. Homicides fall in that group. There were few of those.

Mr. EVANS. Was there an excess among Vietnam veterans——

Colonel WOLFE. As in other studies, we found in the first 5 years after return from Vietnam, there was an increase in these accidental deaths, primarily due to aircraft accidents. But after that first 5 years, that tailed off and dropped to a normal rate.

The similar trends were seen in the studies done by the CDC, the VA and many folks going back as far as World War I and World War II.

Mr. EVANS. Has there been any quantitative comparison of different veterans from different eras, between, let's say, Korean and World War II and Vietnam veterans?

Colonel WOLFE. We have not done that with ours.

Dr. HOUK. In the mortality study of the Vietnam experience, the veteran, there was a 43-percent increase in mortality in the first 5 years in returning from Vietnam to the non-Vietnam veteran.

Mr. EVANS. From these kinds of accidental——

Dr. HOUK. Almost all of that was due to external causes, which is automobile crashes, suicide, homicide and drug related deaths.

Mr. EVANS. Do you have that by subject category? Have you looked at, for that matter, motor vehicle deaths or motorcycle deaths, which might have been suicides?

Dr. HOUK. Well, a single crash of an automobile or a motorcycle is very difficult to ascribe to suicide or not suicide unless you do a psychological autopsy on the individual. But we also reported to this committee last year when there were newspaper stories going around that there were 100,000 suicides in the Vietnam veterans groups since returning from Vietnam. The number is closer to about 9,000, within limits.

If you like, we would be happy to bring that submission back and submit it for the record.

(See p. 135.)

Mr. EVANS. Let me ask you if there have been other studies since that first 5-year period?

Dr. HOUK. Yes. In the second 5-year period, the rates of diseases of deaths were the same except there was a few more drug related deaths, but only two or three more. We are now in the process of doing the 15-year study for the first 15 years after returning from Vietnam.

Mr. EVANS. We are still looking at that? We don't really have it broken down into different categories of suicide, homicide, motor vehicle?

Dr. HOUK. Yes, we do. I just don't have it at the top of my head. It has already been submitted as part of the monogram on the mortality study. I will be happy to re-submit that again.

(See p. 136.)

Mr. EVANS. I understand there were studies that indicate that dioxin exposure leads to irritability and depression in animals. I wonder if anyone is looking into whether that might be a possible explanation for at least that first 5-year period after discharge for this disparity in terms of excess rates of violent deaths?

Dr. HOUK. Unfortunately, dioxin or 2,3,7,8-TCDD specifically leads to a lot of things in animals which we are not seeing in humans. We know the people from Vietnam, from the Vietnam experience study that although a small percentage, more have anxiety, depression and alcohol abuse than do the non-Vietnam vet group. Current illicit drug use is 0.5 percent. That is one-tenth of the age adjusted population percentage for this country.

Mr. EVANS. Thank you. One other brief question relates to the Veterans' Administration's Environmental Hazards Committee. Just about the time that CDC indicated that it could not go ahead with this study, there was a leak to the New York Times that showed a 58 percent higher lung cancer rate and 110 percent higher non-Hodgkin's lymphoma rate among Marines in Vietnam as compared to non-theater veterans. Are you following up on the Marines in that study as a committee to look at the, these incidents of higher rates? If you are, when can we expect results from any follow-up that you are doing?

Dr. YANDERS. The committee does not initiate studies or do studies. It reviews those that have appeared in the literature.

I have not seen any follow-up study on the one which you mentioned.

Mr. EVANS. All right.

Ms. GELBAND. I would just comment that it is being followed up. Actually, the VA initiated four follow-up studies of findings that came out in that first study. One is a mortality study of Marines, based on a larger group than they were able to study in the mortality study.

Second, they have already added deaths for another 3 years. There are now about 60,000 deaths, as opposed to the 50,000 they originally reported on. They are also analyzing deaths among Army veterans who served in I Corps, which is apparently where most of the Marines served.

Lastly, they did a case-control study of non-Hodgkin's lymphoma and Hodgkin's disease, selecting cases and controls from the Veterans' Administration patient treatment file. They gave the results of that study at a scientific meeting, reporting no association between Vietnam service and those two cancers.

The case-control study is not published yet, and we have not reviewed it. I am just stating what they have reported, and emphasize the fact that they have followed up on the proportionate mortality study findings.

Mr. EVANS. Thank you, Mr. Chairman, for the additional time. I appreciate it.

Mr. MONTGOMERY. Thank you.

The Chair would like to close this hearing this morning. We want to thank the panel members for being patient and very helpful. I will now call on Dr. Raymond, who is the head of the staff of our subcommittee on medical care, to ask some technical questions for maybe about 15 minutes.

If the panelists could answer the question fully but hold it down, that would certainly help us out because I made some promises that we would try to finish up this hearing around 12:15 p.m.

Dr. Raymond?

Dr. RAYMOND. Thank you. I believe the intent of the hearing was perhaps more narrow than the scope of questions that have arisen. In particular, we were interested in looking at the link between exposure to dioxin and Agent 0range and adverse health effects. What I would like to do is ask a couple of questions to which you might be able to respond yes or no or agree or disagree.

First, it seems there are two basic steps in research to get at these kinds of questions. The first step is to identify who was exposed, and then secondly, to determine if there was a health effect. Would you agree that that, as simple as it sounds, is what we are about?

Dr. YANDERS. Yes.

Dr. HOUK. Yes.

Ms. GELBAND. Yes.

Dr. STELLMAN. (No audible response.)

Dr. RAYMOND. Taking the first point, and that is who was exposed, which is the one that seems to be giving the most trouble, there are two general approaches to measuring that exposure.

One might be to estimate the exposure based on proxy measures such as geographical location, such as spray patterns, or such as self-report. Would you agree that that is one approach?

Dr. YANDERS. Yes, sir.

Colonel WOLFE. Yes.

Dr. HOUK. No.

Dr. RAYMOND. No?

Dr. HOUK. In the absence of very detailed occupational records, it has been our experience over the last 10 years that where we can measure things in people, that using environmental data and being around things has resulted in a minimum of 40 percent misclassification.

Dr. RAYMOND. Yes, sir. Ms. Gelband?

Ms. GELBAND. I agree generally.

Dr. RAYMOND. Dr. Stellman?

Dr. STELLMAN. I only partially agree.

Dr. RAYMOND. Okay. A second approach which Dr. Houk was getting at might be to actually try to measure that exposure by some sort of physical means such as a laboratory test, such as physical examination of fatty tissue or some other approach. That would be the more reliable approach. Dr. Houk suggest that it would be a more reliable approach.

Would you agree with that?

Dr. YANDERS. Yes, sir, I agree.

Dr. RAYMOND. Colonel Wolfe?

Colonel WOLFE. Yes, I do. In general, where effects, or where exposures are very prolonged and where risks are very high, the use of calculated indices, I think, are more likely to be useful; but in the presence of a short-term exposure, as we are dealing with, a year or less, and with risks that may not be extremely high, I think actual measures is the only way to go.

Dr. HOUK. I agree, Dr. Raymond. But if something caused a 10-fold increase, you don't need an exposure. Any exposure index is going to point it out.

Dr. RAYMOND. Ms. Gelband?

Ms. GELBAND. Well, I would just like to mention in this particular case, in the instance where there is known direct exposure like in the NIOSH study of production workers, what they have found so far is that the ranking given by knowing what jobs people had and how long they were working in those factories agrees very, very well with the blood dioxin levels.

For instance, when that same kind of comparison was made in CDC's validation studies, even people who had relatively high probabilities of having been around spray in Vietnam objectively, say compared to a person occupationally exposed, they were relatively low. And when you looked at the dioxin levels, they agreed with what we saw in the records: the levels were low. And so in this case, at least working backwards, you can assume that if an objective measure of blood dioxin and a subjective measure of exposure agreed, that you could at least use those subjective measures as a reasonable approach. You just have to know whether they agree.

Dr. RAYMOND. Dr. Stellman?

Dr. STELLMAN. I think that dioxin, a positive dioxin finding is indicative of positive past exposure. I don't think that a negative is necessarily indicative of no past exposure; and I believe that the level and the kinds of—the records that are available from military history equal any occupational data certainly that has been used in the past.

Dr. RAYMOND. Dr. Stellman, you and Ms. Gelband have actually anticipated the next question. And that is the existence of health effects. If a laboratory measure, such as the one that exists for measuring blood dioxin level, were to reflect a high level of dioxin, would it be safe to assume that that person has been exposed to a high level of agent orange containing dioxin?

Dr. YANDERS. Definitely; yes, sir.

Dr. RAYMOND. Colonel Wolfe?

Colonel WOLFE. Yes, I agree.

Dr. HOUK. Yes.

Dr. RAYMOND. Ms. Stellman?

Dr. STELLMAN. It depends what their job was, you know.

Dr. RAYMOND. If they have a high level of dioxin as measured by the blood test, would you be willing to assume that they would have been exposed at some time in the past to dioxin?

Dr. STELLMAN. To dioxin, yes. Obviously yes.

Dr. HOUK. Could I correct one thing that Dr. Stellman said? One of the reasons we could not use military records alone, without validation, was because in looking into those records, in each of the companies where we have information on a daily basis, men in that company may be dispersed over 20 kilometers; and so you know where the company is, but you don't know where the precise location of the man was on that particular day.

Dr. RAYMOND. That really is a corollary issue to the existence of the high level as measured by the blood test?

Dr. HOUK. That is right.

Dr. RAYMOND. Okay. Now it seems to me that there would be two general ways of getting at health effects. One would be actual examinations using medical means or laboratory examinations; and the other might be self-report of symptoms or a general opinion of one's own health.

Would you agree that those are two general ways to approach health effects?

Mr. MEADOWS. Yes, sir.

Dr. YANDERS. I agree.

Dr. HOUK. The self-report of everybody that we have ever studied in all the toxic substances issues, people who think they have been exposed always report more adverse health effects than you can validate by medical record or medical examination.

Dr. RAYMOND. But, in fact, there are two general ways to get at the issue of health status. One is some proxy, such as self-report, as opposed to medical or laboratory means?

Dr. HOUK. But self-reports need to be validated.

Dr. RAYMOND. Okay. Ms. Gelband?

Ms. GELBAND. Yes.

Dr. RAYMOND. Dr. Stellman?

Dr. STELLMAN. Yes.

Dr. RAYMOND. If, then, we have the opportunity to look at a group of people who have high levels of dioxin in their blood as measured by a laboratory examination, and perhaps in the presence of supporting occupation or military information, and if we look at them and we find health effects, we would be safe in assuming that there is—depending on how many we found—some association between exposure to dioxin and health effects?

Dr. YANDERS. I would agree completely.

Colonel WOLFE. Yes.

Dr. HOUK. Yes.

Ms. GELBAND. Assuming that the study was well designed and that the comparison group was similar in all respects other than that exposure, et cetera.

Dr. RAYMOND. Well put.

Dr. Stellman?

Dr. STELLMAN. (No audible response.)

Dr. RAYMOND. It seems that that is what we have all been discussing today, is how we get at the question; and while some people have said that there isn't an importance about looking at the methodology of getting there, I think we can't understand the results and the health effects until we understand the pieces that go into gathering the data and analyzing the data. Would you agree with that?

Dr. YANDERS. Yes, sir.

Colonel WOLFE. Yes.

Dr. RAYMOND. And so what we have here are several different approaches, it seems to me. We have the Ranch Hand Study which gathered medical and laboratory examinations to supported health effects, and is now in the process of taking blood dioxin measures to be able to correlate any health effects with levels of dioxin, a year-and-a-half away Colonel Wolfe tells us; we have the CDC that took health status of veterans as verified by medical and laboratory examinations and compared that to people who did not serve in Southeast Asia, not including measured blood dioxin except in the blood validation study where they found that the general ground troops did not have a very high measured exposure; and we have the American Legion study which took self-reported location com-

pared to spray missions and self-reported health status and came up with an association with disease.

Is that a simple-minded, but generally accurate characterization of the kinds of agent orange specific studies that exist—I am not talking at all today about combat-related or other kinds of associations with disease—is that a quick, dirty but reasonably accurate characterization?

Dr. YANDERS. If I followed you correctly, yes, sir; it is.

Colonel WOLFE. I believe that is fair to say.

Dr. HOUK. Yes.

Ms. GELBAND. Yes.

Dr. STELLMAN. I would modify it to say disease or history—history of disease—I don't think that we would be prepared for a cross-sectional study despite everything we heard. If you actually read our papers, we are quite conservative in what we say. We think there is a relationship with a report in history of disease and certain symptom complexes, yes.

Dr. RAYMOND. Two final questions. Would the panel agree that in the perfect world, it would be better to have validated exposure by some chemical and medical means than not?

Dr. YANDERS. Unquestionably.

Colonel WOLFE. Absolutely.

Dr. HOUK. Yes.

Dr. STELLMAN. Depends on how realistic your perfect world is.

Dr. RAYMOND. Would the panel agree it would be better in the most perfect world to have health status corroborated by medical and laboratory examinations than not?

Dr. YANDERS. I think it is absolutely essential.

Colonel WOLFE. Yes.

Dr. HOUK. Essential.

Ms. GELBAND. Yes.

Dr. STELLMAN. Again I think you would have to ask about what the outcomes are that we are talking and what is the purpose of the study and what are the goals. If you are asking that question and it ends up putting a restraining order on the ability to do research, then I don't agree. If you are talking about an infinite amount of money, time, patience, then you want to set up a perfect study, yes, I agree.

Dr. RAYMOND. Is the blood dioxin study useful in any of these exercises?

Dr. YANDERS. I think it is going to be tremendously useful.

Colonel WOLFE. I agree. I think this is the answer we have been looking for for a long time.

Dr. STELLMAN. I don't know.

Dr. RAYMOND. Thank you, Mr. Chairman. I am finished.

Mr. MONTGOMERY. I think one of our panelists did say that sc far the time element on the blood dioxin testing is still viable, that in years past it was still in the blood, showed dioxin, and time is not a factor.

Dr. HOUK. The average half-life is 7.1 years. I think we are very confident of that number in men. We don't know about in children and lactating women, but they are not an issue here. But we have measured dioxin in people occupationally exposed, where the occupational exposure stopped 30 years ago and still have 300, 400,

1,000 parts per trillion. When we measure the Seveso blood serums at 27,000 parts per trillion, when you take some of the Ranch Handers and some of the NIOSH and put that half-life and go back to when they were exposed, you get exposures of 20,000 parts per trillion at the time they are exposed. That frankly gave me a little bit of heartburn because I did not know that was possible. It was nice to get the Seveso, Italy results of blood assays to show that they were at that high, that very high level.

I would like to comment, if I may, Mr. Chairman, in response to Ms. Gelband's question when she modified the answer, provided the study was well done and all confounders were taken care of. That is precisely the reason we chose Army one-time draftees who served during specific years—to have comparable groups. If we found results or didn't find any results, all the scientists in the world would be criticizing us, correctly, if we didn't have as comparable a group as we could have to do our studies.

Mr. MONTGOMERY. Some of us have been talking on the committee, that it would be expensive, but in some cases the Veterans' Administration at the different hospitals might do blood testing for dioxin, and it might help come up with some of the answers. Do you agree with that, Doctor?

Dr. HOUK. If the VA is going to set up blood testing for dioxin, in my view it should be done in one specific location with a dedicated staff and the equipment that they can give quality results. It is not the kind of test that each VA facility, each hospital, should do. It is expensive. It costs the government in excess of $1,000 per test.

With a staff of 16 that we have, we can do on a good week, if nothing goes wrong, 50 tests, and that is the reason that we testified before you before. We said it was impractical to use a dioxin measurement to get the cohort of the people, you had to find 2,000 based upon the capacity to measure dioxin in this world. It would cost $7 billion and take 360 years to do enough dioxin tests to get the cohort.

I think that it would be useful, but I would strongly urge that it be done at one central location, and the blood can be shipped there without any harm.

Mr. MONTGOMERY. Doctor.

Dr. YANDERS. I concur with that. As Dr. Houk pointed out, this kind of analysis is exceedingly difficult and exceedingly sophisticated. It takes a dedicated group of people used to doing this particular kind of test. It is not the same sort of thing a clinical laboratory in a typical VA Hospital could handle.

Mr. MONTGOMERY. Thank you. I would like to thank Mr. Hammerschmidt, the ranking minority member of the subcommittee, and Lane Evans and staff, Dr. Raymond and staff, and especially I would like to thank the panel. You have been very patient and helpful. You have been very, very honest, and we want to thank you for taking the time and giving us this helpful information.

If there are no further comments from the members, the subcommittee is now adjourned.

[Whereupon, at 12:15 p.m., the subcommittee was adjourned subject to the call of the Chair.]

APPENDIX

THE NEW JERSEY AGENT ORANGE COMMISSION AND POINTMAN

The New Jersey Agent Orange Commission was created by the state legislature in 1980. The role of the Commission was to provide assistance to Vietnam veterans and their families concerning Agent Orange, to inform veterans about Agent Orange, to conduct outreach and provide services as practical to veterans, and to conduct research.

Budgetary restrictions prevented the Commission from beginning any research until 1984 when the state authorized a grant of $225,000 for that purpose. The research funds were passed through the Commission to Rutgers University where the project began under the directorship of Dr. Peter C. Kahn of Cook College and Dr. Michael Gochfeld of the University of Medicine and Dentistry of New Jersey, the co-principal investigators.

The research program was code-named "The Pointman Project" as representative of those infantry soldiers that led their squads in Vietnam. It was felt that this name was particularly fitting in describing that Vietnam veterans may be acting as "Pointmen" for society and the health effects that may have been caused by exposure to dioxin.

POINTMAN I

Pointman officially got under way in December 1984 when 6 Vietnam veterans entered Barnart Memorial Hospital in Patterson N.J. to complete 3 1/2 days medical and psychological examinations which included a fat biopsy used to analyze 13 dibenzodioxin and dibenzofuran compounds, including 2,3,7,8-TCDD.

Over the course of the next several months a total of 27 men participated in this examination. This group consisted of 10 persons with a known history of high level exposure to Agent Orange in Vietnam. For each of these we selected a matched control who also served in Vietnam, but had no known herbicide exposure (Vietnam controls). We also sought a matched control who had served in the military at the same time but had no gone to Vietnam. We found only seven suitable "era" controls.

The main focus of the study was a comparison of dioxin levels in the exposed veterans versus the controls. We compared blood and fat dioxin levels for each vet against the levels in his matched Vietnam control. In 9 of 10 pairs the exposed vet had the higher dioxin level in fat and in 6 of 9 pairs (one pair was excluded because of a laboratory mishap) the exposed veteran had the higher dioxin level in his blood.

Comparing the Vietnam controls with the era controls, we found that both had about 5 parts per trillion of dioxin in their fat. The highest value observed in any of the controls was 14.7 ppt. But some of the exposed veterans had over 100 parts per trillion and the average value was above 40 parts per trillion.

The results of Pointman I were published in the Journal of the American Medical Association (JAMA) in March, 1988.

POINTMAN II

Pointman II was funded by a grant of $675,000 from the New Jersey legislature. The first research participants began testing in New Jersey in December, 1987.

In Pointman II we turned our attention to veterans who were not spray handlers and who operated principally ground troops. We began examining a series of small groups, each designated as a pilot project to probe methods for evaluating exposure and, secondarily, to gain some preliminary understanding of health effects for use in a larger study.

ARMY

The first group designated as subjects were men who served with the 2nd. Battalion of the 8th. Cavalry, First Cavalry Division during a fifteen month period in 1968-69. This group was selected after working closely with the Joint Services Environmental Support Group and determining that the portion of Tay Ninh Province where this unit operated was heavily defoliated. In addition to extensive support and encouragement from ESG, we were able to locate the Battalion Commander of this unit, who had kept his Vietnam maps. We were able to plot this unit's activities extensively during this period using standard infantry 1:50,000 maps. We further received assistance from the Army Historical Center and the National Archives to examine the activities and movements of this unit.

Using organizations such as the First Cavalry Association, other veterans groups, press releases and research alerts, we were able to locate a group of individuals who served in this unit. We obtained each man's military record, and conducted an extensive oral history interview with each veteran that participated.

This test group consisted of fifteen members of 2/8, along with 15 matching controls, selected in the same manner as Pointman I.

MARINES

Again, working with ESG, we were able to determine areas of I Corps that were heavily defoliated. We worked closely with Headquarters Marine Corps Historical Division and selected the 9th. Marine Regiment as the unit for study. We selected the period 1967-68 as the exposure period.

In this phase of the program we tested 20 Marines who served with this unit during that time.

NAVY

For this group we used research participants who served with the Navy Mobile Riverine forces in the Mekong Delta during the period 1968-69. We were particularly interested in those units that included activity in and near the Rung Sat Special Zone, and area of heavy defoliation.

This group consisted of 20 participants.

ENVIRONMENT

Each of these groups participated in the ground war in Vietnam. Each operated in both similar and distinctly different ways. By learning more about the operations of these units, we hoped to begin a fuller understanding of the ways ground units could be exposed to Agent Orange. In addition, each of these units operated in distinctly different parts of the country; northern I Corps, western III Corps, and the Mekong Delta. By the extensive examination of these units and the men who participated in the activities of these units, we hoped to develop a more complete understanding of the varying activities in Vietnam.

TESTING

One of the differences in Pointman II is that we no longer hospitalize research participants. Due to the correlation of dioxin measurement in blood and fatty tissue, we no longer perform the fat biopsy as part of the testing and are able to test the men on an out-patient basis. This has resulted in considerable cost savings and a significant morale improvement for both staff and participants. In addition, we have been able to conduct approximately half the testing in the local hotel where we house the participants, eliminating the need for shuttling them to as many test sites.

Since beginning in December 1987, we have tested a total of 60 men. One more test group is required to complete the 70 individuals outlined in the protocol.

LABORATORY RESEARCH

In addition to testing Vietnam veterans, our laboratory at Cook College is conducting a series of studies on blood plasma proteins. The studies are designed to develop a single test to measure most of these several hundred proteins in the blood. It is hoped that development of such a test will be a low-cost method of detecting dioxin related liver damage. Work on this project continues.

POINTMAN II SUMMARY

Pointman II was designed as a 24 month study of individuals who did not directly work with or come into contact with Agent Orange in the course of their normal duties. We attempted to divide the study in such a manner that we would be looking at different types of unit activities and different areas of Vietnam. We hope to complete the final physical testing of research participants by September, 3 months ahead of schedule and announce some preliminary findings by the end of the year.

POINTMAN III

Preliminary efforts have been under way since January with the design of the continuation of Pointman, to be called Pointman III. Once again, a two-year time frame was adopted for the completion of these studies. This phase of the project would be the most ambitious to date, looking into several new areas of concern.

WOMEN VETERANS

Approximately 9000 women served in Vietnam in both military and civilian capacities. There have been many anecdotal reports of ill health among these women, particularly in areas of reproduction. Many of these women served at base camps where defoliation was extensive. Pointman III would study dioxin levels these women, with a projected pilot study of 20 Vietnam veterans matched with 20 Vietnam era controls. Additional OB/GYN testing would also be added to the standard battery of physical and psychological testing given to male participants. The protocol for this study is nearing completion and it is hope preliminary testing could begin in the fall.

In addition to the above, a statistical study of women veterans is being designed.

BIRTH DEFECTS

Many Vietnam veterans are concerned about the possibility of birth defects in their children. A pilot effort is being planned in conjunction with the New Jersey Department of Health to conduct a study of cleft palate/cleft lip. New Jersey has for some time had a state registry of this condition, so it appears a statewide study of this type may be feasible. A protocol for this project is currently under design.

AMERICAN LEGION/COLUMBIA UNIVERSITY STUDY

Commission researchers have taken a great interest in this study, published in December 1988. Preliminary discussions have taken place with the investigators of this study to launch a combined effort using the exposure techniques developed by both this study and with Pointman. A preliminary design has begun that would test approximately 60 men using this combined methodology.

OTHER STUDIES

Commission researchers are currently examining a number of small pilot studies that might be conducted to consider additional aspects of veterans exposure to herbicides.

FUTURE OF THE COMMISSION AND POINTMAN

The Commission and the research effort function solely through the budgetary process of the state of New Jersey. The Commission operates on an annual line-item budget and the research functions as part of a grant process to Rutgers University. The annual funding for the Commission has been approximately $225,000 per year and the research grant had been $675,000 for the period July 1, 1987 until June 30, 1989.

When the state legislature passed it's fiscal year 1990 budget on June 30, 1989, funds were not included for either the Commission budget nor the research. By law, the Commission continues to exist, but as of July 1 there was no funding for office or staff. All employees of the Commission (3), were terminated as of that date.

The research staff are permitted to continue operations until the grant monies are used up. At this writing it appears these funds will last until August 11. The research staff consisted of 4 full time employees and 2 part time employees. The part-time employees were laid-off immediately. The remaining employees are expected to continue to work until August 11 or until they find other employment.

It is unclear at this point what the disposition of the work in progress will be. Arrangements are being made for all files and records to be transferred and stored at Rutgers. The final disposition of the work in progress and these records will be made by the principal investigators and the Commission at a future date.

PERSONAL COMMENTARY

The efforts of the New Jersey Agent Orange Commission should not pass into the archives of history unnoticed. For almost nine years the Commission operated on a "shoe string" budget with limited staff and a host of volunteers. The staff were underpaid even by state government standards. The volunteers came from every walk of life and willingly contributed countless hours of time and energy, providing everything from stuffing envelopes for mail outs and acting as drivers for research groups to professionals providing their expertise in numerous fields "pro bono". Rarely if ever has any agency of government been blessed with such individuals who gave so generously of themselves. This generosity was a result of many people believing in this work and seeking a solution.

Often the work of the Commission and it's research were criticized. Credibility in the form of the 1988 JAMA article and other publications boosted the moral of staff and volunteers and pushed them to greater achievements. Everyone worked countless overtime hours without pay because this issue was one they believed in, one they more than anything wanted to contribute to.

Over the years we have heard from thousands of Vietnam veterans and their families. Of all these contacts, one thing is manifestly clear: Something is tragically wrong out there. Too many veterans are sick. Too many have lost faith in the system they fought to protect. Too many are crying out for answers that do not seem to be forthcoming. These men and women are not "cry babies" as some heartless souls have suggested. They are the cornerstone of this democracy. They are the ones that volunteer to place their very lives on the line when their country calls. They did it then, and most would gladly do it again. They are the backbone of our society. They deliver our mail, work in our factories, drive the trucks and tend to the sick. If we forget and abandon them, we abandon all that is worthwhile about this country.

The New Jersey Commission may be heading for a footnote in the history of this issue. What we may not be able to do we ask the Federal Government to do, as indeed has been it's responsibility from the beginning: Find the answers and take care of those who have protected us. There can be no other moral alternative.

JULY 1989

TESTIMONY OF HELLEN GELBAND, SENIOR ASSOCIATE
OFFICE OF TECHNOLOGY ASSESSMENT
U.S. CONGRESS
SUBMITTED TO THE U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

Update on Agent Orange Exposure in Vietnam and Related Studies

July 10, 1989

Just over a year ago, I testified before this subcommittee on what was known about exposure to Agent Orange in Vietnam. Summarizing briefly, men whose jobs regularly involved handling herbicides--Air Force Ranch Hands and chemical corpsmen, mainly--had exposures high enough to result in persistent elevated body burdens of dioxin. Other men, including some infantrymen, probably had occasional direct exposures when spraying around bases with backpack or truck-mounted sprayers. Most ground troops, however, probably had relatively little exposure. When Congress mandated an Agent Orange study in 1979, and for several years thereafter, this was not the commonly held view. Initially, the biggest design problem for the study was thought to be identifying enough men who had been in Vietnam and were unexposed to serve as a comparison group for the many thought to have been exposed heavily to Agent Orange. Only after several years of painstaking research in the military records, and finally, measurements of blood dioxin levels in veterans, did an altered picture emerge. Research completed in the last year has tended to confirm the validity of blood dioxin levels as a marker for heavy exposure in the past.

The field is not without controversy, however. The most prominent claim that the scenario above does not accurately portray exposure to Agent Orange comes from the American Legion. Their dissent is based their own study, which they believe demonstrates that a large proportion of Vietnam veterans had significant exposure to Agent Orange, and that those exposures are associated with a number of current serious health conditions. OTA reviewed the American Legion study in January 1989 at the request of the House and Senate Veterans'

Affairs committees. We believe that major flaws in the design of the study preclude the conclusions that the American Legion has drawn about exposure to Agent Orange and other herbicides and about subsequent health effects.

Information will continue to come in from studies of Vietnam veterans and from other populations with known dioxin exposure. In the past year, new information on exposure has come from the Ranch Hand Study and from preliminary results of a National Institute for Occupational Safety and Health (NIOSH) study of former production workers exposed to 2,3,7,8-TCDD ("dioxin"). After describing these developments briefly, I will review the studies still in progress, including the Air Force Health Study (the "Ranch Hand Study"); the Selected Cancers Study, being conducted by the Centers for Disease Control (CDC); and the Department of Veterans Affairs (DVA) Proportionate Mortality Study. After that, I will discuss some problems of the American Legion study, particularly relating to the herbicide exposure assessment used, and comment on a recent report updating mortality data for the population around Seveso, Italy, a site of heavy dioxin contamination from an explosion in 1976.

New Information on Exposure to Dioxin

Over the past year, blood from Ranch Hand Study participants (see below for details of the study) was drawn and forwarded to CDC for analysis, which is nearly completed. The results to date show consistently elevated levels of dioxin in Ranch Hands who had the greatest direct contact with herbicides--e.g., men who operated spray equipment in the air and those who cleaned out airplane spray tanks on the ground--and "background" levels (for the U.S. population, "background" is currently considered to be less than about 20 ppt) in those with little or no direct contact. When all the analyses are in, the Air Force plans to reanalyze the 1987 examination results using these blood dioxin levels (and levels extrapolated back to Vietnam service), which should give a more precise estimate of the relationship of health effects and exposure than has been possible previously. The reanalysis should be finished in 1991.

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NIOSH has been studying workers employed between 1951 and 1972 in the manufacture of chemicals known to have been contaminated with dioxin. The 281 workers and 260 non-worker comparison participants were examined for a wide range of physical effects and had blood drawn for dioxin analysis. The workers had been employed at two plants, one in New Jersey and one in Missouri, and had worked for varying lengths of time; the comparisons were matched by sex, age, and race, and came from the same communities as the workers. NIOSH researchers have reported on dioxin levels analyzed thus far, comprising 27 workers and 19 comparisons from New Jersey. The average dioxin level in the workers' blood was 208.2 parts per trillion (ppt); the average for the comparisons was 8.2 ppt, far lower than the workers. Overall, the exposures of these chemical production workers took place earlier than the period of heaviest use in Vietnam (1967-69). The mean end date for workers was 1964, with an average of 4.2 years of exposure (including only days actually worked in production). Within the exposed group, dioxin levels were highly correlated with the length of exposure. Workers with exposures of about two months or less had levels similar to the comparisons (below about 20 ppt), and those with years of exposure ranged up to 717 ppt. In one anomalous case, a worker with 462 days of documented exposure had a unexpectedly low level, 12.2 ppt. Also, a receptionist, assumed to have had no exposure during her two years at the plant, had a slightly higher than expected level of 26.1 ppt (the other receptionist in the study, who had been employed about 15 months, had a level of 11 ppt). Analysis of physical examination findings by levels of dioxin has not yet been completed.

Ongoing Studies

Ranch Hand Study

The approximately 1,200 participants in Operation Ranch Hand, the Air Force fixed wing aircraft program responsible for most Agent Orange spraying, form the largest identifiable group of veterans known to have had significant exposure to the herbicide. The Air Force has

been studying these men and a group of Air Force Vietnam veteran "controls," matched by military occupation and other pertinent characteristics, since 1982, when they conducted their first analysis of Ranch Hand deaths since the war and the first in a series of interviews and physical examinations. Since then, the analysis of causes of death has been updated periodically, the most recent report appearing in April 1989, based on the 74 Ranch Hand deaths that have occurred. Analyses of physical examinations conducted in 1982 and 1985 have been released, and analysis of a 1987 examination is, according to the Air Force, progressing on schedule for release in the first quarter of 1990. Future physical examinations are scheduled for 1992, 1997, and finally, 2002. An additional report, a complete analysis of birth outcomes based on birth certificates and medical records, is nearly complete and should be released in early 1990, according to the Air Force.

Because of the relatively small number of Ranch Handers, and the fact that they are generally middle-aged and healthy, relatively few (epidemiologically speaking) instances of serious disease and few deaths have occurred. The strength of this study is in assessing the possible effects of Agent Orange on diseases that occur more commonly, and also on more subtle, subclinical conditions that may be detected in the extensive laboratory testing that has been part of the study.

Currently and at least for the next few years, it will be impossible to draw any conclusions from the Ranch Hand Study about Agent Orange and cancer, unless there is a dramatic increase in cancers over what has been seen so far. The evidence to date does not suggest an excess of cancers, but the number of cases is too small to rule out a small or moderate increase.

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Selected Cancers Study

The Selected Cancers Study is one of three studies originally proposed by CDC to fulfill the mandates of PL 96-151 and 97-72. (The other two are the Vietnam Experience Study (VES), completed in 1988, and the Agent Orange Study, which proved infeasible.) Because cancers are relatively rare in middle age, the predominant age group of Vietnam veterans, CDC sought to test hypotheses related to Vietnam service and certain specific cancers in a case-control study, a more efficient means of studying rare diseases than is the cohort approach of the VES. Like the VES, however, the "exposure" is to what has been called the "Vietnam experience," and not to Agent Orange. Blood dioxin measurements are not part of this study. (The test had not yet been developed when the study began, and it is uncertain whether blood dioxin determinations in people who already have cancer would be valid, in any case).

If the Selected Cancers Study reveals that having served in Vietnam puts men at a higher risk for developing the cancers under study--soft-tissue sarcoma, lymphoma (including Hodgkin's Disease and non-Hodgkin's lymphomas), nasal and nasopharyngeal cancers, and primary liver cancer--it will be impossible to know whether Agent Orange might be the cause. In the case of primary liver cancer and nasal and nasopharyngeal cancers, in fact, other causes would be more likely suspects. It is known for certain that chronic hepatitis B infection is responsible for most primary liver cancer around the world. This cancer is relatively rare in the United States, but it is the most prevalent cancer in Asia, where a large percentage of the population is infected with the hepatitis B virus. In the Selected Cancers Study, no evidence of past or present hepatitis B infection is available for cases or controls, so infection with it cannot be evaluated as a risk factor. The VES did assess hepatitis B, however, and reported that Vietnam veterans had a significantly higher prevalence (14.1%) of past exposure (though not chronic) than did non-Vietnam veterans (11.1%).

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The idea that some nasopharyngeal cancers may have a viral etiology has been suggested by the worldwide distribution of these cancers and other evidence. The Selected Cancers Study will not have the information to assess this possibility.

The power of the Selected Cancers Study to detect an association with Vietnam service is very good for soft tissue sarcoma and lymphoma, and somewhat lower, but still good, for primary liver cancer and nasal and nasopharyngeal cancers. This good power is based on an assumption that all veterans were exposed to the particular aspect of the Vietnam experience that might be important in causing cancer. If a cancer-causing element of the Vietnam experience were less than ubiquitous, however, the power of the study would be diluted accordingly. It is worth emphasizing, though, that the power of the study is best for soft-tissue sarcomas and lymphomas, the cancers most frequently implicated as associated with phenoxy herbicides.

According to CDC, the full report of the Selected Cancers Study is scheduled for release in spring 1990. Initial analytic problems resulting from AIDS-related lymphomas among the cases have apparently been resolved to the investigators' satisfaction.

DVA Proportionate Mortality Study

The DVA proportionate mortality study was discussed at length at this subcommittee's hearing last June. The clearest findings that provided cause for concern were the excess deaths among Vietnam veterans (compared with Vietnam era veterans who served elsewhere) from motor vehicle accidents, accidental poisonings (including drug overdoses), and other accidents and injuries. Two other findings, however, became the focus of discussion and debate: excess deaths from non-Hodgkin's lymphoma (NHL) and lung cancer among Marine Vietnam veterans. Both of these findings were based on relatively small numbers, but suggested the need for

followup. As I testified last year, the most likely cause of the excess lung cancer deaths is a difference in smoking rates between the two groups. The NHL excess might suggest the presence of an unidentified risk factor limited to Marines, or could be a chance finding.

During the past year, DVA have continued work on this study and undertook specific followup studies on the Marine findings. First, the entire proportionate mortality study has been updated to include deaths that occurred in 1982-84, adding about 11,000 to the original 50,000 earlier deaths. Second, deaths among Army veterans who served in I Corps, where most of the Marines served, have been analyzed separately to see whether the Marine findings applied generally to other men who served in the same part of Vietnam. Third, DVA has conducted a case-control study of NHL and Hodgkin's Disease, selecting cases and controls from the DVA patient treatment file. DVA researchers recently reported at a scientific meeting that no association was found between Vietnam service and these cancers, but no written report of the study is yet available for review. Lastly, DVA is conducting a separate study of Marines, comparing deaths in a cohort of about 10,000 Vietnam veterans to 10,000 Vietnam era veterans. According to DVA, the first three of these efforts should be completed relatively soon, and the Marine mortality study should be completed in about a year. These are all important studies and their results will be of great interest.

NIOSH Dioxin Registry Studies

Results from the NIOSH study of workers from the New Jersey and Missouri plants, mentioned above, will be coming in over the next two years. CDC has now completed most of the dioxin blood assays, and data from the physical examinations are being analyzed by biological system. According to NIOSH, dioxin levels for the complete study cohort, and reports on three biological systems should be finished in fall 1989, with publication in early

1990. A separate part of the study consists of an analysis of birth outcomes to all members of the cohort. This has required collecting hospital and vital statistics records for all births, a time consuming procedure. That part of the study will probably not be completed until 1991.

NIOSH also has been studying the causes of death among all workers in the dioxin registry. About 7,000 production workers with potential dioxin exposure comprise the registry, and in the neighborhood of 20 percent of them are deceased. A rough index of exposure (number of days worked with the possibility of direct exposure) for each worker has been derived from personnel records from each plant. Based on the early results from the New Jersey plant (described above), time exposed appears to correlate relatively well with current dioxin levels, and therefore, with actual past exposure. This study should be completed in late 1989 and published in 1990.

The American Legion Study

The American Legion sponsored a study to examine the health, social, and economic consequences of service in Southeast Asia (SEA). A sample of their members who had served during the Vietnam era were asked to fill out questionnaires concerning their military experiences and aspects of their subsequent functioning and wellbeing. The study was conducted by researchers based at the Columbia University School of Public Health, and the results appeared in five papers published in the December 1988 issue of Environmental Research.

The investigators reported deficits in a number of social, economic, physical, and psychological measures that they related to having served in SEA. They also reported that among SEA veterans, problems appeared to be associated with more extensive reported combat experience, and with having higher scores on an Agent Orange exposure estimate scale. OTA formally reviewed this study in January 1989, at the request of this Committee and the Senate Veterans' Affairs Committee. My testimony is based on that review.

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The American Legion study has major flaws that call into question the validity of the findings reported, particularly those related to herbicide exposure. These flaws include: 1) aspects of the method of selecting the study population and low rate of response to the questionnaire, both of which may have contributed to a lack of comparability of SEA and non-SEA veterans in the study, and possibly lack of comparability of subgroups of SEA veterans (e.g., men who believed they were exposed to herbicides or who were in heavier combat and who have health problems may have been more likely to participate than other men); 2) an unvalidated and probably invalid method for assessing Agent Orange exposure; and 3) an unvalidated and probably invalid approach to collecting health (and possibly other) information about the participants. All epidemiologic studies suffer from some bias, and no methodology is perfect. However, the American Legion study has such serious problems that, even though some of its conclusions might be correct, the evidence produced by the study cannot be relied upon for an understanding of the consequences of having served in SEA during the Vietnam era. Each of the major problem areas is discussed in detail in OTA's January 1989 review. In my testimony, I will speak mainly about problems with the method used to estimate herbicide exposure.

Agent Orange Exposure Estimation Method

The method used to arrive at numeric Agent Orange (and other herbicide) exposure scores for individual participants is described in a 1986 paper by Stellman and Stellman. As have previous attempts at developing an Agent Orange exposure index, this one combines information from soldiers' locations and the computerized records of herbicide spraying (from the HERBS and Services HERBS tapes), taking into account time and distance from spraying. The authors make a number of claims for this methodology, the most general being that it "can be profitably used in most epidemiologic studies of the effects of herbicides on U.S. troops." Further, that "the accuracy and precision of the method are comparable to, or exceed, those

used in many major environmental and occupational studies." They state that "a sizable number of individuals were classified as 'high' exposure," and that the data "make the convincing point that sufficient numbers of troops are available and identifiable for epidemiologic study of herbicide effects."

The American Legion exposure estimation method suffers from more severe problems than did CDC's best attempt at an exposure index, which was ultimately rejected as inadequate. The most serious of the problems with the American Legion exposure estimation method are:

1. Self-reported location data: Nearly 20 years after the fact, veterans were asked to recall each location at which they spent time during their tour of duty in Vietnam. Especially for men who moved around frequently (probably those in combat), this is an almost impossible feat.
2. Locations were chosen from a list of place names provided in the questionnaire. While men might have been near a particular town, large U.S. bases, where many men were stationed, and where combat troops were likely to have been, were not in the middle of towns. The place names may refer to places many miles off, yet it was presumably these actual towns that the American Legion researchers used as points of "location," from which the distances to spray coordinates were calculated. It is impossible to judge the accuracy of this method, and the investigators provide no information to support their claim that the method is "precise and accurate." In fact, it appears to be far less precise than CDC's method of using grid coordinates from military records of troop locations.
3. There is no discussion of missing data, yet there must have been significant gaps in the information reported on the questionnaires. If gaps were ignored, as seems likely, it is possible that reporting a lot of places or accounting for a greater percentage of the tour of duty would produce higher scores. This is one point on which no information is found in the papers.

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4. Any location up to 15 kilometers away from a spray path coordinate virtually any time--including years later--after spraying, is considered in the exposure zone, the scores diminishing with increasing distance from the spray path. The highest exposure score appears to be given for being within 5 kilometers of spraying. The experimental data that exist from trials at Eglin Air Force Base, which, while not necessarily definitive, are the best available, suggest that virtually no Agent Orange would have travelled more than 2 kilometers from the spray line, and even at that distance, the amounts were minuscule. In CDC's analyses, nearly all troop locations that were "within 5 kilometers" of spraying were actually beyond 2 kilometers (i.e., between 2 and 5 kilometers), so even what is considered to represent the highest exposure in the American Legion study would likely have been almost no exposure at all in most instances. While it is entirely possible that some people were within 2 kilometers of spraying, particularly some time after spraying, they would likely be in the minority. The rationale for including distances up to 15 kilometers does not appear to be supportable given the set of facts available.

The investigators do not give examples of other successful occupational or environmental studies that have used less precise and accurate exposure measures than theirs, in support of their general claims quoted above. The herbicide and dioxin studies of which I am aware have had more stringent exposure criteria than did the American Legion study. Several studies have focused on occupational groups with known, direct exposure, including the studies of Swedish foresters, the current NIOSH studies of chemical production workers, and the Air Force Ranch Hand study. Studies of heavy environmental exposure in Missouri and Seveso include groups with known, direct exposure. In no case would a person living 15 kilometers from where herbicides were sprayed be assumed to have had significant exposure, unless some direct contact could be documented. A person living even 5 kilometers away from a plant

producing a dioxin-contaminated chemical would not be considered exposed comparably to workers in the plant, even if some dioxin were entering the general environment from the plant. While everyone acknowledges that conditions in Vietnam were different in many ways, there is no evidence suggesting that a scenario as unlikely as that underlying the American Legion exposure estimation method existed.

The comment that a "sizeable" number of men were classified as having had high exposure may be misleading. Although no description is given of the method used to divide the group into low, medium, and high exposure categories, it appears that divisions were made to create groups of convenient size for analysis. (This conclusion is based on examining the "Agent Orange Exposure Index" distribution in Figure 3 of the first paper.) It is clear that most of the 557 men classified as having had "high" exposure were very nearly the same as those classified as "medium," and that the entire range of scores, except for a few men in a long tail in the high end, was quite tight. Any array of individuals with specific numeric scores, which can vary by even small amounts, is divisible arbitrarily into groups, but doing so is not necessarily meaningful. To give an example, a man who was 10 kilometers from a spray would presumably have a higher score (for that occasion) than a man who was 15 kilometers, but in all likelihood, neither had a significant exposure, even if one is called "high" and the other "medium."

The authors claim a measure of validity for this index because they say that men could not have known, by the information they provided, how they would be classified. But according to data presented in the 1978 paper, men's self-reports of exposure were predictive of their exposure status as calculated. This could be due to the high correlation of the Agent Orange and combat indexes, suggesting that, in general, men who scored higher on the subjective combat exposure index also believed they had been more exposed to Agent Orange. Because of the gross imprecision represented by the Agent Orange index, the idea that it was actually measuring something else is a plausible explanation for the findings.

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CDC's final exposure assessment method, used in their "validation study," was superior to the American Legion method. When CDC arrayed men by their exposure estimates, the range was quite small, with very few who had scores that would be considered high on an objective basis. This lack of clearly defined high exposure was borne out by the results of serum dioxin testing. In CDC's "validation study," the group of men who had served in heavily sprayed areas in Vietnam had dioxin levels no different from a similar group of men who had not served in Vietnam at all. If there were, in fact, large numbers of ground troops with high exposures, it is possible that CDC's method would have identified them accurately. The finding of only "background" dioxin levels in the ground troops contrasted sharply with significantly elevated levels in a group of Ranch Hands with known, direct exposure, providing assurance that a heavily exposed group is easily identifiable from one with low exposure, even 15 or 20 years after the exposure has ceased.

The American Legion study refers to testing for residual dioxin in the body as a means of detecting past exposure as "yet to be validated." It may be true that blood dioxin levels for <u>individuals</u> may not correlate directly with past exposure, but the method is relatively well validated for <u>groups</u> with high past exposure. CDC's validation study, a similar study conducted under the auspices of the New Jersey Agent Orange Commission, the recent Ranch Hand and NIOSH results, as well as studies of heavily exposed Missouri residents, and serum dioxin testing in individuals living in a dioxin-contaminated area near Seveso, Italy, all are consistent with heavy past exposure predicting persistently elevated blood dioxin levels. What remains unknown is the possible range of past exposure that could lead to current levels in the background range, and what the kinetics of elimination are in the background range. These gaps will be filled as the blood dioxin assay is applied more widely.

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Ten-Year Mortality in the Seveso Population

A paper titled "Ten-year mortality study of the population involved in the Seveso incident in 1976," by P.A. Bertazzi and colleagues, appeared in the June 1989 issue of the American Journal of Epidemiology. The study reports on all deaths (almost complete ascertainment has been achieved) that occurred through 1986 in the population living in and around Seveso at the time of and subsequent to a 1976 chemical plant explosion, from which a dioxin-rich cloud settled over the area. For the purpose of health surveillance, the area in which the cloud settled was split into three sections, representing a small highly contaminated area (zone A), a somewhat larger, moderately contaminated area (zone B), and a larger area in which dioxin was still detectable above background levels (zone R). Long-term follow-up of cancer incidence and mortality have continued since the accident.

The paper reports that 27 of 556 individuals from zone A died in the 10 years after the accident; 170 of 3920 from zone B had died; and 1362 of 26,227 from zone R had died. Overall mortality rates and cause-specific rates were compared with corresponding rates for the entire Seveso region of Lombardy. The first five years and second five years of followup are analyzed separately, in addition to the analysis for the entire 10-year period. The abstract of the paper and the discussion claim a number of statistically significant findings, but an examination of the data themselves reveal these interpretations to be somewhat misleading. For example, a significant excess of deaths from cardiovascular disease is reported for the zone A population. Quoting from the paper:

> The increase was particularly notable among males in the first quinquennium and among females in the second quinquennium. Males had a significant increase in chronic ischemic heart disease and cerebrovascular disease mortality.

There were two deaths from chronic ischemic heart disease among the males in zone A, both occurring between 1976 and 1981, giving a statistically significant excess over what was expected. No deaths from that cause were recorded during between 1982 and 1986, which is

clearly less than expected, however, no notation of that appears in the table. Taken over the entire 10-year period, the two deaths do not represent a statistically significant elevation. The five deaths from cerebrovascular disease exceed the expected number for the entire 10-year period, but still constitute such a small number that no conclusion can be drawn from it alone. The zone B and R analyses for cerebrovascular disease show no excess whatsoever; in fact, there were fewer than expected such deaths among females in zone B and males in zone R.

Taking another example, the authors note a "clearly elevated brain cancer mortality among males, first period, and females, second period, in zone R," which they say raises "a hypothesis which warrants further investigation." In total, there were five brain cancer deaths among men and five among women for the entire 10-year period, and for the whole period, this was not significantly elevated, despite the fact that for men, more occurred during the first five years and for women, more during the second. This sort of variation in rates is well within statistical expectations, and should not be accorded particular relevance.

As one would expect from a study with relatively few deaths, a number of subanalyses show more deaths than expected, and a number show fewer than expected. Overall, however, no real differences in either mortality from all causes or mortality in larger categories (e.g., all cancers) is noted. The authors do caution about drawing conclusions from this study, with its inherent size limitations, and state that the results "do not permit conclusively associating any of the noted increased risks with the ICMESA accident." The way the results are presented, however, suggests that major excesses exist for certain causes of death in the Seveso population. An independent look at the data does not support that conclusion. It is, of course, important that surveillance of this possibly heavily exposed population continue, but the mortality data to date do not give cause for alarm.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

before the

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON VETERANS' AFFAIRS

SUBCOMMITTEE ON HOSPITALS
AND HEALTH CARE

Monday, July 10, 1989

10:00 a.m.

Room 334, Cannon House Office Building

Good morning, Mr. Chairman and Members of the Committee. I am Dr. Vernon N. Houk, Director, Center for Environmental Health and Injury Control (CEHIC), Centers for Disease Control (CDC). I am pleased to testify on behalf of the Department of Health and Human Services and further discuss Vietnam veteran and Agent Orange issues.

BACKGROUND

CDC's involvement in these issues began in 1980 with the conduct of a Birth Defects Study among Vietnam veterans. This research effort, supported by the Department of Defense (DOD), the Veterans Administration (VA), and CDC, was separate from the studies mandated by Public Laws 96-151 and 97-72. The results of this Birth Defects Study were published in 1984 and showed that Vietnam veterans, in general, were not at increased risk of fathering babies with major structural birth defects when compared with men who were not Vietnam veterans.

Public Laws 96-151 and 97-72 directed the VA to conduct investigations of Vietnam veterans' health. The first of these laws, signed in December 1979, required a study to assess the possible health effects of exposure to herbicides, primarily Agent Orange, during the Vietnam conflict. The second, signed in November 1981, expanded the scope of the study to allow for the

inclusion of other environmental hazards associated with service in Vietnam. CDC accepted the responsibility for design and conduct of the studies in January 1983 through an Interagency Agreement with the Veterans Administration.

In May 1983, CDC completed and submitted a draft research protocol for scientific review and comment by four groups: the Congressional Office of Technology Assessment (OTA), the Science Panel of the Cabinet Domestic Policy Council Agent Orange Working Group (AOWG), the HHS Advisory Committee on Special Studies Relating to the Possible Long Term Effects of Phenoxy Herbicides and Contaminants (the Ranch Hand Panel), and CDC's own Ad Hoc Review Panel. CDC received comments from these groups by September 1983.

The final protocol for these studies was published by CDC in November 1983. The protocol incorporated modifications suggested by the scientific reviews and stated that the studies were designed to allow for the addition of procedures or questions based on interim analyses of the data or data from sources outside these studies. Three independent, but related, studies comprise the CDC's Agent Orange Projects:

1. The Vietnam Experience Study: a study of the effects of military service in Vietnam.

2. The Agent Orange Study: a study of the long-term health effects of exposure to herbicides in Vietnam.

3. The Selected Cancers Study: a study to determine the risks of specific cancers among Vietnam veterans. This study was designed because the number of these malignancies in the above two studies would not be sufficient to arrive at any valid conclusions.

Other than the Selected Cancers Study, which is ongoing, nothing has changed since Dr. Mason's and my June 8, 1988, testimony before the U.S. House of Representatives Committee of Veterans' Affairs Subcommittee on Hospitals and Health Care. I will summarize our 1988 testimony on the status of the Agent Orange Study, the Vietnam Experience Study, and the National Institute for Occupational Safety and Health Production Worker Study. In addition, I will comment on the American Legion-Columbia University sponsored studies which were published in December 1988 and present a summary of a CDC review of the Seveso Mortality Study. Lastly, I will comment on specific conditions related to pending legislation and provide updated information on the progress of the Selected Cancers Study.

STATUS OF THE AGENT ORANGE STUDY

The Agent Orange Study (AOS) was designed to evaluate the possible health effects of exposure to Agent Orange in Vietnam veterans. Implementation of the AOS depended on development of a scientifically valid herbicide exposure index based on information contained in military records. As cautioned in the 1983 protocol, many of the proposed categorization procedures were untested. Therefore, pilot study assessments were necessary before a final decision could be made to proceed with a full-scale study.

Based on the results of intensive work between 1983 and 1986 by the U.S. Army and Joint Services Environmental Support Group (ESG) and CDC, a Science Subpanel of AOWG concluded in June 1986 that a "scientifically valid study based on military records was not possible without an independent method of exposure verification." The reason for this conclusion was that considerable misclassification of an individual's exposure status was possible; i.e., there was no way, based on records alone, to verify an individual's exposure to herbicides.

During 1986 CDC began to develop a new laboratory method utilizing blood to measure current body burdens of dioxin as an indicator of previous exposure to dioxin-containing substances such as Agent Orange. The CDC scientists were successful with this new method as a more feasible approach for testing groups of individuals than previous methods because dioxin is measured in serum rather than adipose tissue. Also, CDC in collaboration with the Air Force found the half life (the time it takes the body to eliminate half of a substance) of TCDD in humans to be approximately 7.1 years. A protocol for a "Validation Study Comparing Military Records-based Estimates of the Likelihood of Exposure to Agent Orange with Current Serum Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)" was developed by CDC and approved by the AWOG Science Panel and OTA in October 1986.

The results of the Agent Orange Validation Study (AOVS), released in July 1987, showed no association between serum TCDD levels and several different military records-based estimates of the likelihood of Agent Orange exposure. Also, there was no meaningful association between TCDD levels and veterans' self-reported exposure estimates. Among the 646 Vietnam veterans for whom

TCDD levels were obtained, the median TCDD level was 3.8 parts per trillion (ppt), with a range from less than 1 to 45 ppt. The median TCDD level for the 97 non-Vietnam veterans was also 3.8 ppt, with a range from less than 1 to 15 ppt. Two Vietnam veterans had levels above 20 ppt, one with 25 and another with 45 ppt; no non-Vietnam veterans had levels above 20 ppt. The veteran with a level of 45 ppt reported no exposure (military or civilian) to herbicides; the veteran with a level of 25 ppt reported 180 days of indirect military exposure (defined as walking through, or clearing vegetation in, a previously sprayed area), plus one day of home use, but no other exposure. During the telephone interview, both of these men reported their health as "excellent," with no health problems perceived as a consequence of exposure to Agent Orange.

In summary, we concluded that a scientifically valid study of Agent Orange exposure could not be done based on military records. Both the AOWG and OTA concurred with this conclusion based on the results of the AOVS. We further concluded that it was not feasible to establish the cohorts based upon serum TCDD analysis.

The methods CDC used to select individuals and to classify herbicide exposure in the AOVS have been criticized, particularly by persons associated with the New Jersey Pointman Project. The criticism focuses on the so-called "hits" model used to select veterans for study. This model computes for each veteran a "hits score"--the sum of all the occasions for which a veteran's company was within 2 kilometers of an area sprayed by Agent Orange in the previous 6 days. (In this model, a higher score means a greater opportunity for exposure.)

If we had only based our evaluatation on the "hits" model these criticisms might have some basis. However, we also compared serum TCDD levels with several other exposure models, including two which are similar to those being used by the New Jersey group. We found no meaningful association between any of the scores from these models and TCDD levels at the time of the study. In evaluating the potential for exposure, we note that the 646 Vietnam veterans served an average of 320 days in tactical battalions (according to military records information abstracted for CDC by ESG) which operated in the heaviest sprayed area of Vietnam (III Corps) during the peak years of Agent Orange spraying (1966 - 1969). Furthermore, we included all men who, based on the hits score, had the highest likelihood of exposure and also sampled men who had a relatively low likelihood of exposure.

While the AOVS was underway, CDC was also measuring TCDD levels on a group of Air Force Health Study participants (which consists of Ranch Handers and a comparison group). Of the 147 Ranch Handers studied, 25 had current TCDD levels of between 50-100 ppt, 16 between 100-200 ppt, and 5 over 200 ppt; all but one of the 49 Air Force veterans in the comparison group had TCDD values less than 10 ppt. In addition, the Air Force/CDC Half-life Study, a National Institute of Occupational Safety and Health (NIOSH) Pilot study of herbicide production workers, and the New Jersey Pointman Project have all detected substantially elevated TCDD levels in occupationally exposed individuals whose last known exposure occurred 15 or more years ago. We understand that an update of the Air Force serum dioxin studies may be presented in a statement to this committee by the Air Force.

As was stated in our June 1988 testimony, the published results from New Jersey's Pointman Project are consistent with findings from CDC's AOVS. Participants in the New Jersey study who did not handle Agent Orange directly as an occupational duty did not have elevated TCDD levels upon examination in 1987.

Dr. Michael Gochfeld of the New Jersey Agent Orange Commission, and a principal participant in the New Jersey Pointman Project, also testified during the June 1988 House Subcommittee hearing. He agreed with this assessment stating:

> "You have heard Dr. Mason say that the results of the New Jersey and the CDC studies agree, and I think that is very important. They are remarkably close, almost too close if you were going to predict it."

Later in his testimony, Dr. Gochfeld accepted CDC's method of validating exposure to Agent Orange based on serum dioxin levels as a standard. He further stated:

> "It [the AOVS] is primarily an exposure study, and it establishes a methodology for using a blood test as a surrogate or as an indicator [of] past exposure."

The VA and the Environmental Protection Agency (EPA) have recently released results of a collaborative effort measuring levels of 2,3,7,8-TCDD in 3 groups (40 Vietnam veterans, 80 non-Vietnam veterans, and 80 civilian men, all born between 1936 and 1954). The mean levels of dioxin were not significantly different between the 3 groups. They concluded that "the study results suggest that heavy exposure to Agent Orange for most Vietnam veterans was very

unlikely and that there is no readily available and reliable indirect method of assessing exposure to Agent Orange for Vietnam veterans."[1]

STATUS OF THE VIETNAM EXPERIENCE STUDY (VES)

The VES was designed to evaluate possible health effects of the "general Vietnam experience" by comparing the health status of a cohort of male U.S. Army veterans who served in Vietnam with a cohort of male U.S. Army Vietnam-era veterans who served elsewhere. This study was initially designed with three main components: a mortality assessment, telephone interviews, and medical and psychological examinations. Based on interim analyses of the data and the experience of the Ranch Hand Study (related to acquisition of birth records), CDC added to the VES a birth outcome validation component and a semen analysis component.

I will describe the general findings of the VES, starting with the Mortality Assessment component, which was published in February 1987. Then, I will address the morbidity findings which were published in the Journal of the American Medical Association (JAMA) on May 13, 1988.

Mortality Assessment Component of the VES

The VES used a random sample of military records to find 9,324 male U.S. Army veterans who served in Vietnam and 8,989 Army veterans who served in Korea, Germany, or the United States during the same period. All of these men had been discharged alive with a rank of E1-E5 after a single enlistment starting between 1965 and 1971.

We found that for the entire follow-up period (from discharge through December 1983), total mortality among the Vietnam veterans was 17% higher than for the other veterans. Further, the excess mortality occurred mainly in the first 5 years after discharge from active duty, when the death rate among Vietnam veterans was about 45% higher than the rate of non-Vietnam veterans.

Most of the increased mortality was from external causes, such as motor vehicle injuries, suicide, and homicide. After the first 5 years, mortality among Vietnam veterans was similar to that of non-Vietnam veterans, except for drug related deaths, which continued to be elevated.

The overall finding of excess postservice mortality due to external causes among Vietnam veterans was similar to that found among men returning from combat areas after World War II and the Korean War.

Morbidity Findings of the VES

I will discuss the findings of the telephone interview, the medical and psychological examination, and the reproductive and child health components of this study. Since there are no comparable morbidity data from previous wars, it is not possible to compare morbidity data from the VES with data on veterans of previous wars.

Telephone Interview:

In the telephone interview, about 18,000 veterans (whose addresses on their military records date from the late 1960s) were traced. In 1985-1986, we

located 94% of the Vietnam and 92% of the non-Vietnam veterans. Of the men located, 93% of the Vietnam and 91% of the non-Vietnam men agreed to be interviewed, a tribute to their extraordinary spirit of cooperation.

The interviews revealed a broad similarity between the two groups in terms of current demographic and social characteristics, such as education, income, employment rates, and marital status. However, the Vietnam veterans reported more current limitations in activities, more current use of prescription drugs, and a greater prevalence of many types of diseases (e.g. hypertension, urinary tract ailments) and somatic and psychological symptoms (e.g. headaches, dizziness, anxiety). Also, the two groups reported a similar, total number of physician-diagnosed cancers though the number is too small to draw any conclusions. The Vietnam veterans reported more problems with impaired fertility, yet both groups reported fathering the same average number of children.

Medical and Psychological Examinations:

In the examination component, we invited a random subsample of about 42 percent of interviewed men for comprehensive physical, psychological, and laboratory examinations. Physical and laboratory examinations showed few current differences between the two groups, despite the many differences elicited by telephone interview.

For example, there were large differences in skin problems reported during the telephone interview, but on examination all skin conditions, including scars from possible past chloracne, were found with similar frequency.

Overall, hundreds of physical health items and laboratory assays were evaluated as part of the examinations. For most items no statistically significant differences were found between the two groups. The most noteworthy differences were high frequency hearing loss (9.4% versus 6.2% for both ears), stool occult blood (1.3% versus 0.5%), evidence of past infection with Hepatitis B (14.1% versus 11.1%), lower sperm concentrations (15.9% versus 8.1% below reference range), and lower average proportions of morphologically "normal" sperm cells (15.9% versus 11.4% below reference range). Nevertheless, the average number of children fathered per veteran after assignment to primary tour of duty was identical for Vietnam and non-Vietnam veterans--1.6 children.

Psychological evaluation of the men was done through standardized interviews and questionnaires. Although most men in both groups fell within normal limits in these evaluations, current psychological problems [primarily alcohol abuse or dependence (13.7% versus 9.2%), anxiety (4.9% versus 3.2%), or depression (4.5% versus 2.3%)] were more prevalent among Vietnam than non-Vietnam veterans.

About 15% of the Vietnam veterans reported experiencing symptoms which met diagnostic criteria for combat-related Post Traumatic Stress Disorder (PTSD). Combat-related psychological symptoms diminished over time, but 2.2% still experienced episodes of PTSD during the month before examination or 15 or more years after service in Vietnam.

Reproductive Outcome Findings of the VES

Vietnam veterans reported more birth defects and other health problems among their children than non-Vietnam veterans during the telephone interview. However, the children of Vietnam veterans were no more likely to have birth defects recorded on hospital birth records than were children of non-Vietnam veterans. These results of Vietnam veterans reporting more birth defects but finding no differences based on hospital records are consistent with the findings of three epidemiologic studies (the Australian birth defects study, the CDC birth defects study, and the U.S. Air Force Ranch Hand Study) conducted since 1981 on the relationship of Vietnam service and birth defects in children of male veterans.

NIOSH Production Workers Study

NIOSH maintains a registry of approximately 7,000 workers who were employed at 14 plants in the production of chemicals that were contaminated with 2,3,7,8-TCDD. NIOSH is also conducting a mortality study of the workers from all 14 plants which should be completed in FY 1990.

In addition, NIOSH is doing a cross-sectional medical study of 400 living workers from 2 of these 14 plants and an individually matched comparison group of unexposed neighbors. This study is designed to identify effects of exposure to TCDD on hepatic, neurologic, dermatologic, immunologic, reproductive, and psychologic disorders. Interviews were completed on 360 production workers and 325 comparison group members. Physical examinations were conducted on 281 of the interviewed workers and on 260 of the interviewed comparison group. Serum concentrations of TCDD were measured on 279 of the

examined workers to determine the probable extent of exposure to TCDD. TCDD levels were also measured on approximately 120 of the examined comparison group. This study will also be completed in FY 1990.

American Legion/Columbia University Studies

On Veteran's Day, November 11, 1988, a press conference was held by the American Legion and Columbia University to announce the imminent publication of five American Legion-Columbia University sponsored papers reporting on a study examining the health effects of herbicide exposure and service in Vietnam.

These papers, later published in the December 1988 issue of Environmental Research, were based on questionnaires completed by American Legion members. News media reports in advance of publication indicated that the "American Legion Studies" were critical of CDC's approach to validation of military records-based exposure measures through serum dioxin determinations.

Acting on our responsibility to review and evaluate any scientific evidence which might shed some light on the Agent Orange issue, in early November 1988 CDC contacted the American Legion and the authors of the Environmental Research study. We were interested in conducting a thorough scientific review of the study as early as possible and requested advance copies of the publication, the original study protocol, and the study questionnaire. Those items were not made available, and we were not able to conduct the review.

On November 22, 1988, the Congressional Committees on Veterans' Affairs requested that the AOWG (Agent Orange Working Group of the Cabinet Domestic Policy Council) review the American Legion Studies and provide comments with respect to the scientific methods used, the validity of the statistical analyses, and the strength of the studies' findings.

In response to this request, on January 10, 1989, the Science Panel of the AOWG released its review of the American Legion papers and reported the following:

> The data presented in the American Legion report of the Epidemiologic Studies of Vietnam Veterans (Environmental Research 1988; 47:109-209) do not support the conclusions drawn by the authors. The study is seriously flawed due to major problems in study design and execution. First, there is potential selection bias due to non-random sampling and low response rates. Second, there is potential information bias due to poor questionnaire design and the analysis only of self-reported data without external validation, Probably of greatest concern, any observed association between combat or herbicide exposure is confounded by the investigators' use of subjective measures of combat and herbicide exposure. Combat exposure was not validated by comparison with military records. The herbicide exposure index used by the authors has not been validated, and based on the Agent Orange Validation Study and the Ranch Hand Study, does not accurately predict exposure. Because of these problems, the results of the American Legion report are of little or no value in further understanding the Agent Orange issue.
>
> ...The American Legion reports as well as the accompanying editorial imply erroneously that evaluating herbicide exposure in this study is not much different than in retrospective studies of exposure to workers where individual exposures are not measured. The analogy is misleading because in well-conducted occupational studies, one knows from objective records that the employee was in an area of potential exposure and that workers are exposed during operations. In contrast, in the American Legion study, we do not know if veterans were within miles of a sprayed area, and we do not know if any dose, let alone a measurable dose, was received...

> ...For self-reported health outcomes, the results are similar to those obtained with the VES questionnaire. As with the American Legion study, almost all outcomes in the VES were reported more often by Vietnam veterans than by other Vietnam-era veterans. Those Vietnam veterans who reported either handling herbicides or having more combat experience also reported higher rates of most outcomes.
>
> Most of the verifiable self-reported conditions, however, were not substantiated by objective evidence obtained during the physical examination.

We are also aware that an OTA Review of the American Legion studies has been conducted.

Recently Completed Seveso Mortality Study

A mortality study of the population exposed to TCDD in the 1976 industrial explosion in Seveso, Italy was published in the June 1989 issue of the American Journal of Epidemiology.

In the study abstract, the authors make unjustifiably strong statements on a purported statistical association between TCDD exposure and relative risk of several cancers. These statements are not reliable, however, because of improper methods of statistical analysis and inadequate attention to the limitations of the study. Even though the study says that there is an increased risk in some cancers, many of these are based on only one case being found. Reliable inferences on increases in mortality rate cannot be made based on a single case. The authors performed multiple hypothesis tests without adjusting the significance probability, which means that five (5) percent of the hypothesis tests will be declared statistically significant when the association is actually due to chance. This is recognized by the

authors in the discussion section of the study, which is written with considerably more caution than the abstract. A copy of our review of that paper is enclosed.

It should be noted that immediately following the Seveso accident, Italian authorities were assisted by several national and international technical commissions in assessing adverse health effects in the Seveso population. During these Seveso studies, residents underwent extensive medical examinations from 1976 to 1985, and the only abnormal finding detected in a small segment of the population was chloracne.[2-5]

In April 1988, a group of U.S. and Italian scientists convened to further examine the Seveso incident. Using a methodology developed by CDC to measure TCDD in human serum, blood samples collected in 1976 on a few Seveso study participants were analyzed by CDC. CDC reported the results of these analyses in the December 9, 1988, issue of the Morbidity and Mortality Weekly Report. (A copy of this report is enclosed.) The TCDD levels detected in some of these samples are the highest ever reported in humans, up to 5,000 times the background levels. The three highest levels detected were from children who had developed chloracne, but no other known adverse health effects.

Dr. Paolo Mocarelli of the University of Milan recently presented a detailed report on the Seveso Birth Defects and Morbidity Study at the Fourth National Environmental Health Conference in San Antonio, Texas, on June 23, 1989. The findings from the Seveso Studies concerning birth defects; clinical,

neurological, immunological, and dermatological conditions; and exposure assessments were presented. To date, no significant excess of spontaneous abortions, perinatal mortality, low birthweight babies or birth defects has been detected. Of the over 600,000 laboratory determinations, no differences in abnormalities were detected between the TCDD exposed and non-exposed populations. Chloracne was the only clinical finding associated with the level of TCDD contamination. Cancer studies are continuing. We will forward a copy of his report as soon as it becomes available.

Specific Conditions Related to Pending Legislation

I am aware of pending legislation proposing that non-Hodgkin's lymphoma, and certain other conditions be considered as compensable in Vietnam veterans. In presenting the data in these areas from the VES, I want to caution that the number of specific types of cancer are too few for drawing conclusions.

One confirmed lung cancer case was identified in the Vietnam group compared to two confirmed lung cancer cases in the non-Vietnam group.
In my June 1988 testimony I noted that a review of all cases (both living and deceased) of non-Hodgkin's lymphoma (NHL) reported by participants in the VES was able to confirm seven cases in the Vietnam group and one in the non-Vietnam group.

Further clarifying information regarding these findings was conveyed by letter dated June 23, 1988, to the Chair and Ranking Minority members of the House and Senate Committees on Veterans' Affairs. The letter recommended cautious interpretation of the findings, as follows:

Although the difference between these numbers is statistically significant (p=.04), other points need to be considered before biologic significance is assumed. First, the result could still be due to chance given the enormous number of comparisons made in the VES. Second, the NHL cases are not homogeneous in regard to cell-type. For example, two of the Vietnam veterans had Burkitt's lymphoma, a type of lymphoma which is exceedingly rare in the United States and is thought to have a different origin from other non-Hodgkin's lymphomas. Third, the time of diagnosis should be considered. One of the Vietnam veteran cases was diagnosed with NHL while serving in Vietnam, while two of the other Vietnam veterans were diagnosed within 3 and 4 years of leaving Vietnam. Since evironmentally related cancers usually exhibit a longer latent period than observed in these veterans, it is doubtful whether these "early cases" are related to military service. A fourth point to consider is the "expected number" of NHL cases in the two groups.

Based on average annual age-specific U.S. incidence rates reported by the National Cancer Institute (SEER, 1973-1977), 3.9 cases of non-Hodgkin's lymphoma would be expected in Vietnam veterans and 3.5 cases would be expected among the non-Vietnam veterans.

While these results show more cases than expected in the Vietnam group and less than expected in the non-Vietnam group, this comparison should be interpreted cautiously given the methodolgic differences between SEER and the VES.

Two recent studies in Kansas and Nebraska by Dr. Shelia Hoar Zahm of the National Cancer Institute have indicated an association of NHL with the occupational use of herbicides by farmers.[6,7] In both States, the herbicide showing the association was believed to be 2,4-D, which is not contaminated by 2,3,7,8-TCDD (dioxin).

Because studies of Vietnam veterans have to date failed to indicate that many veterans were exposed to Agent Orange (a mixture of 2,4-D and 2,4,5-T), it would not be inconsistent with Dr. Zahm's results to find no association of NHL with Vietnam service, but the final determination awaits the completion of the CDC Selected Cancers Study.

Progress on the Selected Cancers Study (SCS)

The Selected Cancers Study (SCS) is continuing on schedule; it is a collaborative effort of the Selected Cancers Cooperative Study Group, consisting of the CDC, eight tumor registries, and four pathology review panels. The SCS is a population-based, case-control study examining the relation of military service in Vietnam to six types of cancer: Hodgkin's disease, non-Hodgkin's lymphoma (NHL), soft tissue and other sarcomas, nasal cancer, nasopharyngeal cancer, and primary liver cancer. All males with the cancers of interest who were born between 1929 and 1953 and who resided at the time of diagnosis in the geographic areas covered by the eight participating tumor registries were eligible for the study. The exposure of concern is service in Vietnam, not exposure to Agent Orange. The reason for this is that, as discussed earlier, attempts to validate herbicide exposure based on military records or veterans' self reports have been unsuccessful. Because of the numbers involved, the power of this study to detect an association of Vietnam service is very good for soft tissue sarcoma and lymphoma and somewhat less for nasal, nasopharyngeal, and primary liver cancers.

As of April 28, 1989, the latest date for which a progress report is complete, we have data on approximately 65% of the cases who will comprise the final study population. A small percentage of this data has not yet been "cleaned up", i.e., checked for inaccuracies, inconsistencies and missing information. We anticipate that the final study pool will consist of approximately 1000 confirmed cases of NHL (not including those with an AIDS-related diagnosis), more than 350 cases of Hodgkin's disease (again excluding those with an

AIDS-related condition), nearly 350 cases of soft tissue and other sarcomas, 60 cases of nasal cancer, 75 of nasopharyngeal cancer, and more than 120 of primary liver cancer. An analysis of NHL and Hodgkin's disease will be done on all cases with the exclusion of those with AIDS, and a separate analysis will be done including those cases with AIDS. The Institute of Medicine (IOM), National Academy of Sciences Review Committee concurs with this approach. We anticipate more than 200 AIDS-related NHL cases and more than 20 with Hodgkin's disease and AIDS-related conditions from the entire study group which includes both veterans and nonveterans.

Our staff has been conducting preliminary analyses on the partial data set as it has accumulated over the past 9 months and has been presenting these analyses to the IOM committee; therefore, we anticipate a much abbreviated time between receipt of data and availability of the final analyses.

The final reports could be available for review by the IOM and OTA by the end of February 1990. A report could be released to Congress one month later, if the release is prior to submission for journal publication. This schedule also assumes no major additional reanalyses as a result of the IOM and OTA reviews.

If an interim report is requested, this would result in a four-month delay in the completion of the final reports. Such an interim report would necessarily be based on a partial data set and, therefore, may not be helpful in terms of policy or legislative development. In order to have reports prepared for external review in early December, CDC staff estimate that the number of cases

available for analysis would comprise approximately 75% of those cases expected upon completion of the study. In addition, the preparation of interim analyses would delay the completion of final analyses because all available staff will concentrate on analysis rather than completion of data cleanup. CDC estimates that production of these interim reports will delay the completion of final reports for review by the OTA and IOM until June 1990. These reports could be released to Congress approximately one month later (assuming the reviews recommend no major additional work) if the release is scheduled before submission to peer review process required for journal publication.

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Comments on the paper: Ten-year Mortality Study
of the Population Involved in the Seveso Incident in 1976
Pier Alberto Bertazzi, et. al.

This paper is a mortality study of the Seveso population who were exposed to dioxin from an industrial incident in 1976. According to the paper, "The aim of this analysis was not to evaluate causal association of TCDD exposure with specific health outcomes, but rather to provide a comprehensive and coherent picture of the pattern of mortality in the population affected by the accident." However, the authors make unjustifiably strong statements in the abstract on a purported statistical association between dioxin exposure and relative risk of several cancers. These statements are not reliable because of improper methods of statistical analysis and inadequate attention to the limitations of the study recognized by the authors themselves in the discussion section of the paper.

In the exposed zones, a decrease in overall mortality and overall cancer mortality was found

The authors fail to emphasize that in this mortality study, all cause mortality is less in each of the three exposed zones compared to the unexposed reference zone (exposed zones A 4.86%, B 4.34%, R 5.19% compared to unexposed reference zone 5.45%). The authors noted but did not emphasize that overall, "the relative risks for malignancies as a whole tended to be below 1.00." From data presented in the paper, the decreases in overall mortality and cancer mortality can be seen but their statistical significance cannot be calculated.

The mortality data collected in this study are extremely important and this cohort should continue to have extended and detailed followup with appropriate statistical analysis.

Improper statistical analysis

- The authors performed multiple hypothesis tests without adjusting the significance probability which means 5% of the hypothesis tests will be declared statistically significant when the association is actually due to chance. The authors state that they analyzed 118 causes of death, for each sex, for each of three exposure zones, for two separate five-year periods and an overall ten-year period. Not counting the overall ten-year period tests, this would amount to 1416 hypothesis tests for significance which was determined at a 5% level using 95% confidence limits. Consequently, about 70 associations (.05 X 1416) would be improperly found to be statistically significant when they were actually due to chance.

  From the paper, it is not clear if all 1416 tests were able to be done, but even if only 500 were done, 25 associations would be improperly found to be statistically significant. This is an important number because for the two separate five-year periods, only 23 associations were found by the authors to be significant which is actually less than the 25 associations expected on the basis of chance alone.

The statement in the abstract that the elevated mortality from certain cancers "did not appear to result from chance" is therefore not correct; but rather, the elevated mortality from certain cancers is very likely due to chance. This statistical analysis problem can be simply fixed by adjusting the significance probability for multiple hypothesis tests, e.g. using the method of Bonferroni (Miller, R.G. Simultaneous Statistical Inference, Springer-Verlay, New York, 1981) and the data can be reanalyzed.

- Confounding factors for causes of death beyond age and sex are not included in analyses. These are likely to have an effect on estimates of mortality rates by cause.

Design and interpretation limitations

- Of all the 193 persons with chloracne from dioxin exposure, not one has died of cancer or any other cause.
  These persons are the ones with assured heavy dioxin exposure or increased sensitivity to dioxin. Any effect of dioxin would be expected to be much more probable in this group.

- For the full ten-year follow-up period, the statistical significance of cancer associations in the higher exposure zones is always based on only one cancer case.
  For the full ten-year followup period, mortality from four cancers was reported increased in either zone A or zone B (the higher exposure zones). Each one of these mortality increases was based on only one cancer case. Reliable inferences on increases in mortality rate cannot be made based on a single case. For the full ten-year followup period, there were no other increases in cancer mortality in either zone A or zone B. Some cancers had reported increases in the two five-year periods but these did not achieve significance over the total ten-year followup.

- The authors note that the exposure definition used in this study is a "poor surrogate of exposure" to dioxin. Accurate exposure classification is crucial to reliable interpretation of this type of data.

- The single death in zone A from biliary carcinoma occurred 7 months after the industrial explosion which means it is unlikely due to exposure. Also, a separate publication in 1981 listed this death as not biliary carcinoma but pancreatic adenocarcinoma which spread to the biliary tract, liver and lung (Facchetti et. al., Forensic Environ. Appl. 1981; 1:1406-44). This one biliary carcinoma is the basis for the abstract statement of association of biliary cancer with dioxin exposure.

CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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International Notes

Preliminary Report: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure to Humans – Seveso, Italy

At approximately noon on Saturday, July 10, 1976, an explosion occurred during the production of 2,4,5-trichlorophenol in a factory in Meda, about 25 km north of Milan, in the Lombardia region of Italy. A cloud of toxic material was released and included 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Debris from this cloud fell south-southeast of the plant on an area of about 2.8 km^2 (700 acres), including parts of the towns of Seveso, Meda, Cesano Maderno, and Desio. The size of the contaminated area was estimated primarily by measuring TCDD in the soil; additional criteria included the presence of dead animals (e.g., birds, rabbits, chickens) and detection of dermal lesions among persons in the area. The contaminated area was divided into three zones (A, B, and R) depending on the concentration of TCDD in the soil (Table 1). An additional zone, Zone S, outside the contaminated area was examined as a control zone.* Zone A, the most heavily contaminated section, was further divided into seven subzones, A1–A7, based on increasing distance from the factory. The total amount of TCDD deposited in the contaminated area was initially estimated at about 165 g (*1*); subsequently, it has been estimated to be at least 1.3 kg (*2*).

Within 20 days of the explosion, the Italian authorities had evacuated the 211 families (735 persons) from the area later defined as Zone A and had taken immediate measures to minimize the risk of exposure to residents in nearby areas (primarily

*Zone R was originally thought to be a reference zone, but on subsequent detection of TCDD concentrations in soil, Zone S was added.

TABLE 1. Distribution* of TCDD contamination in soil† – Seveso, Italy, 1976

Zone	Population	Size (acres)	Soil sampling square (m^2)	TCDD concentration (μg/m^2)	
				Mean	Highest
A	735	198	2,500	230.0	5477.0
B	4,699	665	22,500	3.0	43.9
R	31,800	3,532	22,500	0.9	9.7

*These data may be underestimated by approximately 25% (*2*).
†Measured in a soil sample, 20 cm of depth, taken at the center of a square.

TCDD – Continued

those in Zone B). The Italian authorities were assisted by several national and international technical commissions in assessing adverse health effects. Residents of zones A, B, and R underwent extensive medical examinations from 1976 to 1985; chloracne, detected in a small segment of the population, was the only abnormal finding (*3–6*). Only one potentially exposed person was measured for TCDD; she was a 55-year-old woman residing in a portion of Zone A (mean TCDD soil concentration of 185.4 $\mu g/m^2$), who died from pancreatic adenocarcinoma 7 months after the explosion. Her TCDD whole-weight levels varied from 6 parts per trillion (ppt) in blood to 1840 ppt in adipose tissue[†] (*7*).

In April 1988, a group of U.S. and Italian scientists convened to further examine the Seveso TCDD incident. Since more than 30,000 serum or plasma samples (volumes of 1–3 mL) had been collected from residents of the four zones from the end of July 1976 through 1985 and stored at –30 C (–22 F), the group agreed to assess whether methodology developed at CDC to measure TCDD in human serum (*8*) could be used to measure TCDD in these low-volume samples. This methodology, a lipid-based measurement highly correlated with paired measurements of TCDD in adipose tissue ($p = 0.98$) (*9*), has been used to evaluate U.S. Army veterans (*10*), U.S. Air Force Operation Ranch Hand veterans (*11*), and occupationally exposed persons (D.G. Patterson, Jr., et al., unpublished data).

The preliminary Seveso study evaluated serum samples from five Zone A residents who developed the most severe types (III or IV) of chloracne; four Zone A residents who did not develop chloracne or other health problems (in 1976, each was ≥15 years of age); and five persons from Zone S. All these samples had been collected in 1976 and were sent without identification to CDC for analysis. These samples were analyzed for TCDD (*8*) on both a whole-weight and a lipid basis, using triglycerides and total cholesterol data provided for those samples by the laboratory of the hospital of Desio-Milan to calculate total lipids.

The TCDD levels detected are the highest ever reported in humans (Figure 1). The three highest levels are from children who developed chloracne. Levels for the other two chloracne cases were similar to those in residents without chloracne. TCDD was not detected in four of the five controls. In one control, a level of 137 ppt TCDD on a lipid basis was detected; this value may represent either an actual level or the detection of a residue of <1% from a sample analyzed immediately before this sample.

Reported by: P Mocarelli, MD, Institute of General Pathology, Univ of Milan and Hospital of Desio, Milan; F Pocchiari, PhD, Instituto Superiore di Sanita, Rome. N Nelson, PhD, New York Univ Medical Center, New York, New York. Center for Environmental Health and Injury Control, CDC.

Editorial Note: Little is known about TCDD exposures and adverse health effects in humans. However, these Seveso samples are unique in that they were taken in proximity of time to an acute human exposure to TCDD. Thus, they and the subsequent samples allow for correlating TCDD levels and adverse health effects, if any, and for determining the half-life of TCDD in humans. This population has no apparent adverse health effects other than chloracne (*4*).

These serum measurements confirm overt exposure to TCDD in those persons tested who resided in Zone A. The levels are of the same magnitude as those found in occupational studies (*12,13*) that estimate initial TCDD levels by extrapolating to

[†]Levels of TCDD in serum or adipose tissue of the general population are <20 ppt.

TCDD – Continued

the time of last exposure (by assuming first-order kinetics and a half-life of 7 years) (*14*). Although the three highest TCDD serum levels occurred in persons who developed chloracne, no threshold level for chloracne is obvious.

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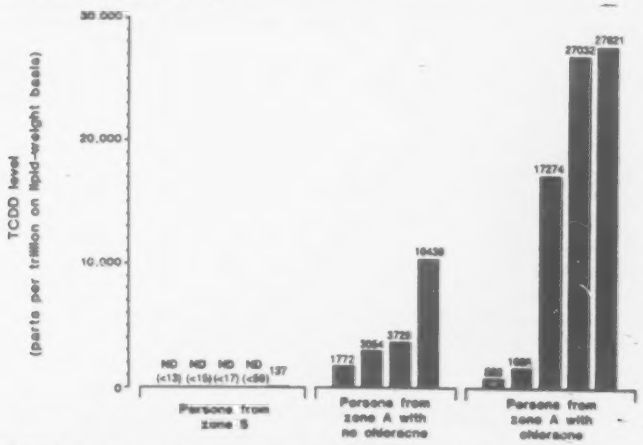
FIGURE 1. Serum TCDD levels* of Zone A residents (with and without chloracne) and Zone S controls – Seveso, Italy



*Levels of TCDD in serum or adipose tissue of the general population are <20 ppt.
ND = Nondetectable at specified levels.

TCDD – Continued

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Testimony of

Mr. Oliver Meadows
Chairman, Veterans' Advisory Committee
on Environmental Hazards

and

Arnson F. Yanders, Ph.D.
Chairman, Scientific Council
Veterans' Advisory Committee on Environmental Hazards

Mr. Chairman, it is a pleasure to be here today to provide you with a brief description of the activities of the Veterans' Advisory Committee on Environmental Hazards, particularly as they relate to the issue of the health effects of exposure to Agent Orange.

I would like to provide you first with a brief history of the Committee. It was established pursuant to Public Law 98-542, the Veterans' Dioxin and Radiation Exposure Compensation Standards Act. The Committee's membership consists of 4 lay members and 11 scientific members. The scientific members serve as a Scientific Council which makes findings and evaluations regarding pertinent scientific studies relating to the adverse effects of exposure to herbicides containing dioxin. I have been very impressed with the caliber of the individuals who have served on the Committee and the dedication of the members. They have tried to be responsive to questions presented to them and to offer the best advice they can consistent with their understanding of the scientific literature. There is active participation by every member of the Committee, both lay and scientific. Through the collegial discourse which occurs, consensus opinions and recommendations are arrived at.

I would like at this point to defer to Dr. Yanders, the chairman of the Scientific Council who will provide you with a discussion of the activities of the Scientific Council.

Dr. Yander

It is a pleasure to appear before you today to provide you with an overview of the activities of the Scientific Council of the Veterans' Advisory Committee on Environmental Hazards. As Mr. Meadows said, the Scientific Council is comprised of eleven members from a variety of scientific disciplines and backgrounds. The Council consists to two panels, a panel which addresses the issue of the health effects of exposure to dioxin and a panel dealing with the issue of the effects of exposure to ionizing radiation. The chairman of the Dioxin Panel is chaired by Dr. Ted Colton of the Boston University School of Public Health and the Radiation Panel is Dr. Warren Sinclair of the National Council on Radiation Protection.

The Council operates, as Mr. Meadows stated, in a collegial manner. Prior to each meeting, the Department of Veterans Affairs forwards to the Chairmen of the two panels a number of materials for review by the Council. These materials come from a comprehensive search of the scientific literature conducted primarily by VA employees but materials may also be submitted by other sources such as members of the Advisory Committee, Committees of Congress, individual members of Congress, or from veterans service organizations. The chairman of each panel reviews the materials and makes an initial decision as to whether the particular paper is relevant to the concerns of the Committee. If it is, then the chairman assigns the paper to one or two reviewers. In making the assignments, the Chairman will consider such factors such as whether the paper presents new findings; whether it is a review or analysis of previously published findings; and whether the paper appeared in a peer reviewed scientific journal or in some other format. Taking these factors into account, the Chairman will assign one or two reviewers to the materials presented. Two reviewers would be assigned if the material clearly warrants the Council's attention and one reviewer if the material was of questionable value. The single reviewer would then exercise his judgment concerning the relevance of the material to the work of the Committee. In any event, all materials are provided to every member and at the meeting of the Committee an ample opportunity is provided for sole reviewer papers to be discussed if in the opinion of the reviewer discussion is warranted. In any case, the more significant papers are discussed at length.

A brief presentation is made of every paper with two reviewers. The reviewers are asked for their assessment of the materials assigned to them. Following each presentation there is an opportunity for comments or questions regarding the paper under discussion. Then the members arrive at a consensus concerning the relevance of the material to the veterans' concerns, whether the conclusions expressed in the material are supported by the data reported, and whether VA's guidelines concerning compensation should be changed in light of the particular material reviewed either singularly or in the context of previously considered materials.

From time to time, the Council has been asked a specific question about a particular disease's relationship to dioxin or Agent Orange exposure. Essentially, the same process is engaged in. The Chairman of the Dioxin Panel assigns a member to lead a discussion of the question presented following which the Council arrives at a consensus and prepares a response which is acceptable to all members.

As you know, there was recently a decision holding that VA and the Committee applied the wrong standard in attempting to determine whether it would be appropriate for VA to award compensation claims based upon exposure to Agent Orange. The Committee concurred with the determination of VA that sound scientific and medical evidence did not establish a cause and effect relationship between dioxin exposure and porphyria cutanea tarda, soft tissue sarcoma, or any other disease except chloracne. The court stated that the requirement for a cause and effect relationship was stricter then had been intended by Congress. The court found that the Congress intended VA to make a finding of whether there existed a significant statistical association between dioxin exposure and a subsequently appearing disease.

The Secretary asked Mr. Meadows to convene a meeting of the Advisory Committee to assist in the development of criteria by which it may be determined whether there exists a significant statistical association between two separately occurring events, in other words, between exposure and the onset of disease. Mr. Meadows consulted with me and we determined it important to respond to the Secretary's request as soon as possible. Accordingly, a special panel of the Committee was convened and it met on June 26 to consider a proposal designed to carry out the court's order. It is my understanding that the comments of the Committee were considered by VA and that a proposed rule has been published for public comment. When the comment period ends, the panel will be reconvened to consider the comments received by VA, whatever comments other Committee members may have made, and the response of VA to those comments. We will offer our advice and recommendations to VA and VA will then publish its final rule. In November, the full Committee will meet and will assess the scientific literature in light of the standard articulated in the regulation.

Mr. Chairman, I know you have asked for the assessment of the Committee of the relevant scientific literature at this time. I think you will understand if we respectfully decline to provide you that assessment because of the pending change in the appropriate standard for judging the literature. I would hesitate to speculate on what the Committee's position will be after it applies that standard or what recommendations it may make to VA in light of the standard. I do want to assure you that the Committee will enter into this process with an open mind and will take very seriously the charge to reconsider the scientific literature and to make whatever recommendations we then believe are appropriate.

TESTIMONY BEFORE THE U.S. HOUSE OF REPRESENTATIVES

COMMITTEE ON VETERANS' AFFAIRS

Subcommittee on Hospitals and Health Care

July 11, 1989

Jeanne Mager Stellman,PhD

Steven D. Stellman,PhD

At the request of the Committee on Veterans' Affairs Subcommittee on Hospitals and Health Care, we are submitting testimony on our appraisal of trends in research findings on the health and well-being of Vietnam veterans, particularly with respect to Agent Orange.

As background information for the Subcommittee, one of us, Jeanne Mager Stellman, holds a doctorate in physical chemistry and is an Associate Professor of Clinical Public Health at Columbia University and a Visiting Associate Professor in Occupational Health at the University of Medicine and Dentistry of New Jersey. I have just been appointed by the Trustees of the John Simon Guggenheim Memorial Foundation to a Fellowship for the period between July 1, 1989 and June 30, 1990 to devote myself to the study of a chemical systems approach to toxicology. I have taken some time from that work to respond to the Committee's request to appear. In addition, I am the editor of the academic journal *Women and Health* and the author, co-author or editor of four books, 20 chapters or monographs, approximately 40 peer reviewed scientific articles, and numerous abstracts, technical letters, newspaper columns and invited keynote speeches and presentations in the field of occupational and environmental health. In addition to winning a Guggenheim Fellowship, I was among the first seven recipients of a five-year National Cancer Institute Preventive Oncology Academic Award and was chosen by Ms. Magazine as one of "Eighty Women to Watch in the 80's."

I have served in many advisory capacities to government agencies and professional organizations including an Office of Technology Assessment Panel on Reproductive Hazards in the Workplace and a participant in the Office of Technology Assessment's conference and publication of Automation in the Office. I served for four years as Chair of the March of Dimes Taskforce on Reproductive Hazards in the Workplace and as a consultant to the World Health Organization and a visiting expert at the Occupational Safety and Health Branch of the

International Labour Office of the United Nations. I have been on the Technical Review Committee of the National Institute for Occupational Safety and Health (Centers for Disease Control) criteria documents for benzene, sulfur dioxide, mercury and cadmium and have served as a peer reviewer and site visitor for the establishment of its Educational Resource Centers (1978-9).

Prior to that I chaired the American Chemical Society's Taskforce on Benzene and served for six years on its Committee on Chemical Safety and its Taskforce on Safe Laboratory Practices. I have been an expert adviser and continuing professional education lecturer for the American Hospital Association, as well as an expert consultant to the Tennessee Valley Authority, the Port Authority of New York and New Jersey, the American Lung Association, the American Cancer Society, the American Occupational Health Nurses Association, the National Cancer Institute's Expert Panel on Women and Smoking (1984) and its Merit Peer Review Committee for Cancer Control (1979-1981), among other consultative professional roles.

I believe I have been asked to testify before this Subcommittee because Steven Stellman and I have been a scientific consultants to The American Legion for many years in the area of the health and well-being of Vietnam veterans.

Steven D. Stellman, who cannot be present today, holds a doctorate in physical chemistry and is currently Assistant Commissioner for Biostatistics and Epidemiologic Research for the Department of Health of the City of New York where he is responsible for the Bureau of Vital Records, Offices of Biostatistical Analysis, Office of Epidemiologic Surveillance and Statistics and he administers more than $364,000 in contracts from the Centers for Disease Control. Prior to assuming this position in June of 1988, he was Assistant Vice-President for Epidemiology of the American Cancer Society (National Division), and Associate Director of Cancer Prevention Study II, a 6-year prospective study of 1.2 million

men and women. Dr. Stellman is concurrently an Adjunct Associate Professor in the Department of Community Medicine, Mount Sinai School of Medicine in New York and has held numerous other academic appointments.

Steven Stellman is the author of more than fifty peer-reviewed scientific publications in the field of epidemiology, cancer, prevention and veterans' health. He also has authored or co-authored twenty-five technical papers in theoretical biophysical chemistry.

Dr. Stellman has served extensively in advisory capacities to government agencies, including the New York State Commission on Dioxin. He has been a member of the National Institutes of Health special study section on chemoprevention trials and on smoking interventions. He has served on the International Joint Commission Workshop on Epidemiology and Great Lakes Pollution, and has served on the National Academy of Sciences/National Research Council Committee on the Carcinogenicity of Cyclamates. He has been a member of the American Chemical Society Advisory Committee on Peer Review and is currently an Advisory Board member of the Public Health Graduate Program of the Robert Wood Johnson School of Medicine/University of Medicine and Dentistry of New Jersey.

Both Steven Stellman and I belong to numerous professional organizations and both are currently serving in the capacity of Exposure Consultants to the Special Master of the Agent Orange Veterans Payment Program and will soon join the advisory board of the Michigan Commission on Agent Orange.

Recently we completed and published a series of articles on the health and well-being of a random sample of Vietnam veteran members of the American Legion. We undertook this study, in part, because we had developed and published a method for utilizing the computerized records of spraying of herbicides in Vietnam, the HERBS tapes and had demonstrated the ability to classify veterans

into groups with differing levels of likelihood of having been exposed to herbicides.

In 1983 we pilot-tested a questionnaire on a random sample of American Legionnaires who lived in South Dakota, and, based on results of this pre-test, in January, 1984, sent questionnaires to a random sample of Vietnam veteran Legionnaires in Ohio, Indiana, Pennsylvania, Minnesota, Maryland, and Colorado. These studies were carried out with the collaboration of John Sommer of The American Legion, and with an advisory board consisting of Columbia University faculty and other experts. Dr. Barry Snow collaborated on the post-traumatic stress disorder component of the study.

Each study component was carefully designed to take advantage of up to date research on factors that have influenced Vietnam veterans' lives. For instance, "Legacies of Vietnam," a Congressionally mandated study, found relationships between combat stress and numerous outcomes, so we chose to consider combat a primary variable. For other psycho-social outcomes we relied on well-established scales, such as the Psychiatric Epidemiology Research Interview (PERI) scales for behavioral problems, which was developed by colleagues at Columbia University in a team lead by Dr. Bruce Dohrenwend and a scale for measuring combat intensity developed by Dr. Charles Figley of Purdue University.

The health effects questions in those sections of the questionnaire dealing with health reflect plausible outcomes in light of both human and animal studies on dioxin and phenoxy herbicides, as well as commonly felt concerns about possible effects of exposure to herbicides.

The most important measurement we had to develop by ourselves was an estimate of exposure to Agent Orange. We have had the original HERBS tape since 1979, and have developed a method for assigning to individual veterans an index of exposure probability. This method was first presented at an open meeting of the American Public Health Association in Montreal in 1982, and has since been

published in the *American Journal of Industrial Medicine*. The only modification to the published method used in the American Legion study was the supplementation of the original data with several thousand new spray coordinates, including back-pack and helicopter operations, from the SERVICES HERBS tape.

The five papers that make up The American Legion - Columbia University Vietnam Veterans Study were published as the entire December, 1988, issue of the scientific journal *Environmental Research*, and run to 98 printed pages. We understand that the Subcommittee has received a full copy of the published articles describing the study and its findings. We can obviously no more than summarize specific findings briefly, and must refer the Committee members to the complete journal issue for our full report. The technical references to the papers mentioned here are contained therein.

The cross-sectional survey of randomly selected members of The American Legion in six states who served in the U.S. Armed Forces during the Vietnam Era was conducted by a mailed questionnaire. A total of 6,810 veterans returned questionnaires to us. Of these, 42% had served in Southeast Asia, and 58% had not. The latter group had experienced very little combat, and are the study controls, although most outcomes are also stratified by combat and/or herbicide exposure among veterans who served in Southeast Asia.

Combat stress was evaluated by a previously validated eight-item scale. Exposure to Agent Orange and other herbicides was estimated via an exposure probability index previously developed by the authors which uses an algorithm based on the combined Air Force and Joint Services HERBS files of spray data. Both combat and Agent Orange exposure exhibited distinct, meaningful distributions among Vietnam veterans with service in Southeast Asia and were also correlated with each other ($r = 0.24$). Our analysis demonstrates conclusively that mere presence in Vietnam cannot be used as a proxy for exposure to Agent Orange.

Categorization of Vietnam veterans according to herbicide exposure can be successfully accomplished, based on an existing detailed herbicide application data base. This analysis, together with the consistent dose-related results obtained in this series of papers on health and behavioral effects, demonstrates the utility of questionnaire-derived herbicide and combat exposure measures for epidemiologic study of Vietnam veterans.

One aspect of the study was devoted to analysis of social and behavioral consequences of service in Southeast Asia. Using validated scales for behavioral affect and for the exposure measures for combat and herbicides, a wide range of adverse effects was observed. Men who faced high levels of combat intensity were found to be at greater risk for divorce and for generally being less happy and satisfied with their lives, their marriages, their roles as fathers, and as sexual human beings. Although in this population they have reached comparatively high levels of education, they earn significantly less money than peers of their same age and educational attainment. Vietnam veterans returning from combat were found to exhibit higher levels of behavioral disturbances, with mean scores for depression, anxiety, irritation, feelings of helplessness, and physical signs of depression — significantly worse than noncombat peers. The lifestyle of combat veterans also continues to place them at greater risk for poor health. They smoke, drink, and use prescription drugs at rates significantly greater than the other veterans in this study. Combat veterans have had a significantly poorer rate of reduction and cessation of smoking and drinking than others in this population. Evidence is also presented which shows that for some of the behavioral outcomes measured, a negative interactive effect of concurrent exposure to herbicides is present.

The relation between combat stress, DSM-III-defined post-traumatic stress disorder (PTSD), and a variety of behavioral factors was also examined in this large nonclinical population. Among the 2,858 randomly selected American Legion

members who had served in Southeast Asia, the frequency of PTSD and the extent of symptoms developed varied with the severity of criteria used for determining extent of traumatic exposure. The PTSD rate ranged from 1.8 to 15.0% of the total sample, depending on whether "exposure" to combat was defined relatively narrowly or broadly. A distinct linear dose-response relationship between combat stress and a quantitative measure of PTSD intensity was observed. The frequency of PTSD diagnosis was not affected by the presence of either physical or mental health problems which predated military service. A strong, stable relationship was found between combat stress and PTSD intensity for cohorts with differing intervals since the experience of combat trauma, which persisted up to 20 years after discharge from the military. The data thus support a broader approach to defining the existence of other behavioral outcomes as residual effects of combat. Implications of these findings and the importance of treating veterans with varying presentations of PTSD are discussed in the study.

History of diagnosed illnesses, medical symptoms, and reproductive outcomes and their relation to combat intensity and herbicide exposure were studied. Heart disease, venereal disease, and benign fatty tumors were reported significantly more often by Vietnam veterans than by controls. Combat intensity was significantly dosage-related to history of high blood pressure, ulcers, arthritis and rheumatism, genito-urinary problems, nervous system disease, major injury, hepatitis, and benign fatty tumors. Agent Orange was significantly dosage-related to history of benign fatty tumors, adult acne, skin rash with blisters, and increased sensitivity of eyes to light. Rates of the latter two conditions and of change in skin color were especially elevated in men whose military occupations involved direct handling of herbicides. Five "symptom complex" scales were constructed via factor analysis to measure degrees of feeling faint, fatigue or physical depression, body aches, colds, and skin irritation. Means of all five scales were significantly higher in

Vietnam veterans compared to controls, and in herbicide handlers compared to nonhandlers. Both combat and Agent Orange exposure were significant, independent predictors of each of the five scales. Neither combat nor Agent Orange exposure was associated with difficulty in conception, time to conception of first child, or to birthweight, or sex ratio of offspring, but maternal smoking was strongly related to reduced birthweight. The percentage of spouses' pregnancies which resulted in miscarriages was significantly higher for Vietnam veterans than controls (7.6% vs 5.5%, $P < 0.001$). Logistic regression analysis showed that Agent Orange exposure and maternal smoking were both independently and significantly associated with miscarriage rates in a dose-related manner.

We also examined the data to determine patterns of usage of Veterans Administration health facilities, as well as attitudes toward the VA and experiences at these facilities. Thirty-six percent of those who had served in Southeast Asia had used VA health facilities, compared with 18% of men who served elsewhere. Among Southeast Asia veterans, combat level was an important predictor of extent usage of VA facilities for problems of both physical and mental health. Combat level was also associated with lack of basic and major medical insurance. While men with lower incomes tended to make greater use of VA mental health facilities, nearly one-fourth of mental health users had family incomes above $30,000. Despite their greater usage of the VA, men with higher combat levels expressed lower feelings of security about this agency, and rated its staff less helpful and of lower quality than did men who experienced lower levels of combat. On the other hand, higher combat veterans thought themselves better informed about VA services. Men who had gone to the VA for mental health assistance reported a disturbingly low frequency of having been asked basic questions that relate to possible diagnosis of post-traumatic stress disorder (PTSD), questions related to combat, which may be one of its etiologic factors, or other questions relating to their military history. Because

combat level in Vietnam veterans is a major determinant of both attitudes toward and utilization of VA health facilities, the VA as well as other health agencies which deal with Vietnam veterans should be especially sensitive to this factor, and should take it into consideration when evaluating veterans' physical and mental health.

Convergence of Findings

Because epidemiological studies result from 'unplanned natural experiments,' they generally lack the rigorous controls of laboratory studies, such as animal toxicological experiments. It is commonly acknowledged in the field that a single epidemiological study, no matter how well designed and carried out, cannot stand alone, and most certainly cannot lead to inferences of cause and effect. Such inferences can only be arrived at by examining the convergence of many epidemiological studies of different designs, carried out by different researchers, involving different populations. Only in such circumstances can one be confident that hidden or un-noticed biases and errors are minimized or eliminated.

A number of studies already published are available for comparison with our own. These include the *Vietnam Experience Study* conducted by the Centers for Disease Control, the National Readjustment Study, conducted by Research Triangle Institute, and the Air Force Health Study.

The CDC's *Vietnam Experience Study* involved a random sample of 15,288 veteran Army enlisted men, of whom 7,924 had served in Vietnam. Other Centers for Disease Control studies on Vietnam veterans have either been abandoned as unfeasible (Agent Orange Study) or have not yet been completed (the selected cancers study). In the Vietnam Experience Study, assessment of combat and herbicide exposure effects were not study goals; comparisons were mainly between Vietnam and non-Vietnam veterans. Despite this major methodological limitation in design which fails to differentiate the study population by the major independent variables of interest, the Vietnam group still differed significantly from the controls

in a large number of outcomes and in patterns strikingly similar to those observed by us in the areas of:

-Psychosocial well-being -- depression and anxiety, post-traumatic stress disorder, and other psychological problems);

-Physical health -- history of hypertension, chloracne, other skin problems, liver conditions other than cirrhosis and hepatitis, fertility problems, possible clinical left ventricular hypertrophy, possible chest X-ray abnormalities, hearing loss, peripheral neuropathy, evidence of past hepatitis;

-Laboratory findings: abnormal gamma-glutamyl transferase, fasting glucose, thyroid-stimulating hormone, occult stool blood;

-Reproductive health -- low sperm count and abnormal morphology;

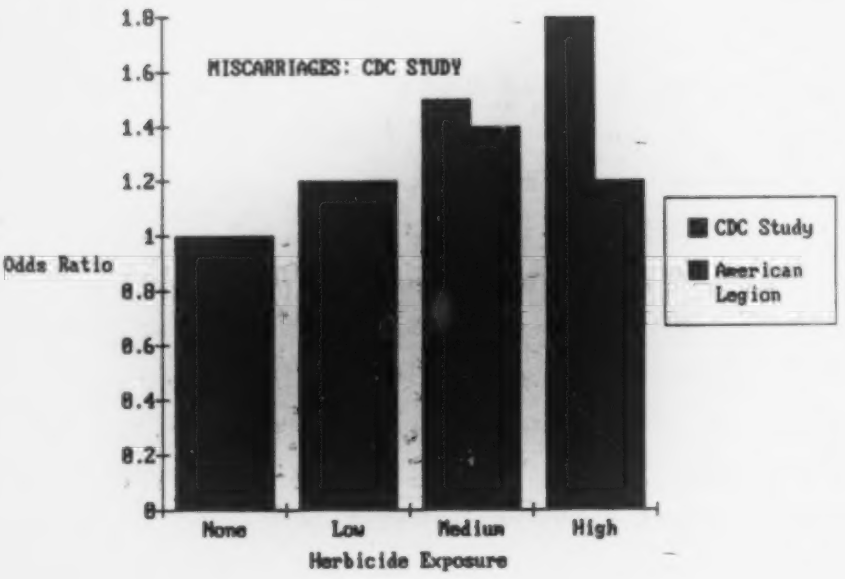
-Increased birth defects: nervous system anomalies, musculo-skeletal deformities, anomalies of the integument, and hydrocephalus

-Increased miscarriage rate (Agent Orange Index dose-related and see attached figure).

The Air Force Study's interim report (February, 1988) showed statistically significant differences between Ranch Hand personnel and controls in six of eleven targeted clinical areas: increased cancer, increased birth defects, psychological changes, hepatotoxicity, cardiovascular changes, and endocrine changes.

We were extremely gratified by the results of the recently released Research Triangle Institute *Contractual Report of Findings from the National Vietnam Veterans Readjustment Study*, which confirms and, indeed, expands our findings among the rather homogeneous group of American Legionnaires to the broader spectra of social, ethnic, racial and sex groups that participated in the Vietnam war. The study's director has stated in public that he has "never seen two studies conceived, conducted and carried out so differently" arrive at such strikingly similar results.

Both the RTI study and our study (see particularly papers I and II in the


MISCARRIAGES: CDC STUDY
Odds Ratio
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
None
Low
Medium
High
Herbicide Exposure
CDC Study
American Legion

series) show clearly that failure to stratify the population by level of combat experience in essence obscures most physical, psychological and social effects that could be attributed to the Vietnam experience.

Cancer and Other Mortality

In addition to these multiple-outcome studies which have dealt with clinical and psychological endpoints, a growing body of literature has focused on cancer as a possible outcome of exposure to phenoxy herbicides. This work has been fueled by studies which show that dioxin causes cancer in laboratory animals.

At least four studies have shown an association between exposure to phenoxy herbicides and soft tissue sarcomas: two Swedish studies of agricultural and forestry workers (Hardell and Sandstrom, 1979; Eriksson et al., 1981), a Danish study of herbicide manufacturing employees (Lynge, 1985), and an Italian study of rice-field workers (Vineis et al., 1986). A Veterans Administration study of soft-tissue sarcoma (Kang et al.) purports to show no relationship with Agent Orange exposure, but close examination shows no credible measure of exposure and too few subjects with a credible latency to permit meaningful analysis. Other studies have, however, found no relationship and each of these studies is referenced in our recent publications to which the Subcommittee has already been referred.

Four other studies have shown a relationship between exposure to phenoxy herbicides and non-Hodgkin's lymphoma: one from Sweden (Hardell et al., 1981), a study of farmers and forestry herbicide applicators in Washington State (Woods et al., 1987), a study of New Zealand agricultural workers (Pearce et al., 1985), and a National Cancer Institute study of Kansas farmers (Hoar et al., 1986).

We also wish to comment on the recently published mortality data from the population exposed to TCDD in the 1976 industrial accident in Seveso (June 1989 issue of *American Journal of Epidemiology*.) This study has already been criticized by Dr. Vernon Houk of the Centers for Disease Control before the U.S. Senate

Committee on Veterans Affairs. Since our study of American Legionnaires also shared the privilege of an onslaught of unjustified criticism by the CDC before the ink on the paper it was printed was dried, we believe it useful for us to provide our perspective on the Seveso study.

First, Dr. Houk raises the always handy argument of multiple comparisons, that is, if one studies 100 outcomes, 5% will be significant at the 5% level. The implication of this criticism is that the authors of the Seveso study (who are highly respected and skilled Italian epidemiologists) went on a 'fishing' expedition, trolling through the data until they came up with positive findings. In fact, any mortality study *must* involve multiple comparisons if it is going to look at the multiple causes from which people die. The test of a well-designed and executed study is whether the initial hypotheses were set up appropriately and whether sufficient and appropriate controls were used. In the case of this study, the answer is unequivocally yes.

Dr. Houk also raises the objection that conclusions are being drawn from single cases. That is true -- but one actually *expects* little else from a population this small -- only 211 families lived in the most heavily contaminated zone and some 3,000 people in the next. *And*, many of these people were children who have an even lower expectation of developing cancer than adults.

In keeping with the way that our study was treated by the CDC and Dr. Houk, the very words of the researchers are misrepresented. The authors are accused of exaggerating their abstract. Here is what they say:

> "...However, no definite patterns related to exposure classification were apparent. Merely suggestive increases in soft tissue tumors and melanoma were also noted. Liver and breast cancer mortality tended to be below expectations. Interpretation is hampered by the short observation period, small number of deaths from certain causes, and poor exposure definition."

Mr. Chairman, we believe this quotation from the abstract stands as a model

of utmost caution and circumspection, and can in no way be considered as exaggerated.

New results from the Agent Orange Veterans Payment Program:

Finally, Mr. Chairman, we would like to take this opportunity to share with you some new findings that arise from our work with the Agent Orange Veterans Payment Program. During the course of acting as exposure consultants, we began to note what appeared to be an unusual distribution of deaths among those applying to the fund. The actuaries for the claims administrator were encountering a disability rate approximately 15% above actuarial prediction and the levels of exposure appeared to be about 10% higher than we had predicted from our earlier studies. Further, it appeared that we were receiving an overrepresentation of claims from certain smaller sized military units.

Based on admittedly superficial and highly preliminary calculations, we sought and received permission from the Eastern District Court and the Special Master to investigate the issue further. The American Legion agreed to paying all costs of codification and data processing so that no Payment Program costs would be engendered.

Mr. Chairman, we have just calculated the initial results of our examination of the first 3,000 deaths among the claimants. In collaboration with Dr. Paolo Boffetta, a Fellow at Columbia University and a visiting scientist at the American Cancer Society, we have observed a very unusual distribution of deaths, particularly of some cancers. These data must be treated very cautiously since it is not clear yet what all the biases in the data base are. We have carried out a proportional cancer mortality and have calculated significantly elevated rates for soft tissue sarcomas and borderline significantly elevated rates for nasopharyngeal cancers, which may be highly elevated among blacks. The numbers here are too small to assure stability. We have found death from cancer of the tongue to be elevated but at a

borderline significance level.

Based on these findings we believe it prudent to continue this research based on a larger number of death claims. We also plan to link these deaths to their military exposures, which, of course, has not been done in the previous studies of Vietnam veterans described above.

Finally, Mr. Chairman, now that we have provided our perspective on the CDC's criticisms of the latest Seveso study, we would also like to take the opportunity to provide to you our response to the criticisms of our study that were orchestrated by Dr. Vernon Houk of the Centers for Disease Control. We believe that our credentials speak for themselves and that the concordance between our findings and those of RTI actually make no response necessary. But since these criticisms have been delivered in writing to this Subcommittee we would like to enter our response into the Subcommittee's records as well.

We thank you for this opportunity to present testimony and hope that we are entering a new era of just compensation for the victims of this nation's latest war, the men and women in the heavy combat zones and those who may have suffered from chemical exposures.

Response to CDC Criticisms of the American Legion-Columbia University Study of Vietnam Era Veterans

Summary:

Apparently a selected group of technical experts were asked to *'review the American Legion-Columbia University Vietnam Veterans Study for study design, sampling, responses rates, and analytic methods that the authors used to cope with flaws'* (Feinleib memo, p 1). Members of the panel thus perceived themselves to have been charged primarily with the task of finding fault rather than providing an objective scientific critique of the whole of the findings, as well as the methodology used to arrive at the conclusions.

The inherent bias in this approach is manifested in the reviews by the absence of perspective on the meaningfulness of the data, their consistency and their relevance to the health of veterans. When, despite their destructive mandate, several of the reviewers did add positive comments about the study and its implications, the cover memoranda have purposefully chosen to omit them (Sweeney comments, p. 4, Lybarger memo, Young memo).

The negative, destructive, 'hatchet-job mandate' is consistent with the following basic premises under which the Government appears to be operating with respect to the health and well-being of Vietnam veterans, summarized in the Houk memorandum:

1. There have been no real health or psychological effects in Vietnam veterans attributable to their Vietnam experience.

2. Any effects observed must, therefore, be due to either a flawed methodology or to misreporting by the veteran. Throughout the review under consideration it is repeatedly asserted that the veterans, the researchers and The American Legion have probably misrepresented data and may even have lied. Some reviewers, like J. Karon, politely alluded to the possibility of "good faith" misapprehension of questions or selective recruitment of subjects. Others were less subtle. Nancy Stroup pointedly mentioned *"The potential for intentional exaggeration of exposure is also clear."*

3. According to the government, there is only one way in which to determine whether a veteran was exposed to herbicides: by a blood test for levels of dioxin (TCDD). The fact that they feel that they have not been able to validate the comparison between exposures and military records at a 100% concordance level, (as opposed to the high level of correlation that they actually did achieve), **gives them the rationale to dismiss any and all studies, including The American Legion's, that use any other method of assessing veteran exposures in Vietnam.** (This is precisely the logic articulated by Dr. Robert Worth, formerly Chief Scientist of the CDC Agent Orange Studies, in his letter to Dr. Houk, and by Dr. Houk in his cover letter to Don M. Newman, Chair, Domestic Policy Council, AOWG). The clinical criteria of retrospective blood assays, in lieu of using the vast stores

of spraying and troop movement data available for study, are nothing short of an attempt to bamboozle the public and the independent scientific community. It amounts to a scientific sham.

4. The critiques contain wide-ranging attacks on our use of *standardized* questions and scales for assessing combat exposure, scales which were adopted from previous studies such as those of Figley and *Legacies*. A major finding of those studies, as well as ours, was that *combat is the principal determinant* of a wide variety of physical, mental health, and social effects. Despite these well-known findings, combat was essentially ignored in the CDC's VES. It is possible that CDC found it necessary to invalidate our use of the combat variable in order to camouflage its failure to investigate what seems to be an obvious concomitant of the military "experience."

5. It appears to us that there is great reluctance in the CDC to participate in open scientific inquiry and processes. Just as the scientific community has been denied a full description of and access to the massive amounts of data on troop locations, so too the CDC has rejected the opportunity to engage in real scientific debate. It conducted a closed door review, which only became known to the researchers when we read about it in the daily newspapers. When the editor of *Environmental Research* had specifically offered to open the pages of the journal to any and all comments and criticisms by the CDC, they refused (Landrigan memo, 11/28/88).

Specific Responses to Criticisms Levelled

Because so many of the reviews are fraught with the same errors and because they all (coincidentally?) seem to cover the same major points, we have chosen to answer the key objections together, citing individual reviewer comments, where appropriate and helpful.

Sampling:

A recurring criticism is that we have drawn a nonrandom sample and have failed to provide demographic information on the nature of the nonrandom sample. It does not matter how many times we are accused of not having carried out a random sample, it *was* a random sample, as described fully on pages 114-115. Houk cites non-random sampling as one of the two most severe flaws in the study design. He is wrong. As stated, volunteers did *not* enroll members, postcards were *not* used to select members, lists of names were randomly generated and the only purposive selection that took place was to choose more men who had served in Vietnam from among the random pool of Vietnam era veterans. We simply cannot make a more clear statement than this.

Strawman Argument #1: Failure to Cite the CDC's Vietnam Experience Study:

We are criticized for failing to cite the Vietnam Experience Study (VES) (Worth, Hobson, Barnes, Sweeney). That study was published in May, 1988. The so-called 'validation study', the blood analysis of only 643 veterans, was published in September 1988. Our papers, as is clearly stated on the title page of each of them, were submitted in November 1987, except for the PTSD paper, which was submitted in January 1988. We would hope the reviewers would have had sufficient professional experience to know that by May 1988 our papers were virtually in galley form. (EPA reviewer Donald Barnes goes even farther and suggests we should have cited "pending NIOSH studies"!)

Nevertheless, given the amount of consternation that our failure to cite the reviewers' work has caused, we would like to point out that had the VES been available for background and comparison, we would have been very pleased to note just how consistent our findings are with those of the VES. Despite differences in design and study populations, the VES and the American Legion study had remarkably similar results for skin conditions, prevalence of PTSD (15% in both studies), hepatitis, heart disease, anxiety or depression, and miscarriage risks (odds ratios: VES 1.3, AL 1.35). Most importantly, as we point out below, the VES confirms the utility of self-reports as a source of veteran health data.

Strawman Argument #2: Representativeness

Barnes, Stroup, Calle, O'Brien, and others commented extensively that The American Legion study could not be considered representative of all Vietnam Veterans. We concur, and have never claimed to carry out a study representative of all veterans. Each paper's title describes it as a study of American Legionnaires. With regard to other veterans, we consider this study to be a **best case** analysis, since those men who have had the social, psychological and financial wherewithal to join The American Legion are demonstrably better off than so many other veterans, particularly those of minority groups who assuredly suffer the additional impact of discrimination. Not a single reviewer, even those who claimed to be concerned with confounding, saw fit to remark that the very homogeneity of the study population represents a powerful reduction in possible confounding by socio-economic factors.

The Issue of Self-Reports and Survey Data:

One of the keystones of the criticisms levelled at the study is that survey data and self-reported health status and combat experiences are completely unreliable and so sullied by 'recall bias' that it is unusable in any way, shape or form. This indiscriminate rejection of the fundamental principles of practically all survey research contradicts the basis of even the CDC study. Houk's memo falsely states that the CDC study found that 'objective evidence' from medical exams did not corroborate the self-reports from the veterans, whereas their published report states that

> **"Within each cohort, the prevalence of reported medical problems among those examined was similar to the prevalence in the total telephone interview. Odds ratios based on examination results were similar to those based on results of the telephone interview." (JAMA 259, 2708-2714, May, 1988)**

Response Rate:

The second most serious flaw cited by Houk and others is the response rate. In fact, *our response rate is comparable to that of the CDC's so-called "validation study,"* in which serum samples were obtained from 66% of Vietnam veterans and from 48% of non-Vietnam veterans.

Questionnaire Construction and Reliability of Measures:

The questionnaire was carefully constructed from our own past work and from other widely recognized studies of combat and psychological health and well-being. Exhaustive references are given in the papers, yet somehow these are not satisfactory to the reviewers. One reviewer Robin Morris, with no more than a wave of the hand, dismisses over two decades

of research and hundreds of publications, when she denigrates the PERI scales, which are considered the gold standard in psycho-social and psychiatric survey epidemiology. She shows her hand when she gratuitously and inappropriately sets up psychiatric DSM-III measures of clinical psychiatric disease as the required criteria for health and well-being analysis in a general, non-patient survey population.

Combat Scale:

The combat scale receives severe attack, particularly as to its construction (Brann memo, Stroup comments). We did not invent this scale, but adopted it from well-established studies of leading investigators, whose work we cited. The statistical reliability of the scale is 0.98 (about as high as one can achieve) and the scale's ability to predict a wide variety of effects that are consistent with those accepted by the non-biased, independent scientific community speaks for itself.

We reiterate point 4 of our summary above: it seems to be an essential tactic for the CDC to destroy the validity of the combat scale in order to protect the premise of their own study in which they failed to measure and utilize this central variable.

As public health professionals we would like to comment on the subjective meaning of the dismissal of the utilizability of the widely accepted combat scale. The CDC's (and, in correspondence, the VA's) attack on the variable, combat, goes deeper than study methodology, and has profound implications for public health policy with respect to veterans. The scale consists of eight questions including queries about how often a man observed his fellow soldiers killed or dead, how often he himself had killed and how often he had found himself in a life-threatening situation. No reasonable person would seriously question a study's validity based on the faint possibility that most veterans could not accurately recall such incidents.

That the government's scientists, (such as Dr. Lawrence Hobson, Director of the VA Environmental Medical Office, in his submission to Dr. Houk) do question a veteran's ability to recall or, more important, to tell the truth, about such experiences, clearly and unequivocally demonstrates the lack of respect they have for veterans. It typifies the inherent anti-veteran biases they carry, and underscores the inappropriateness of the team assembled by the government to carry out research on Vietnam Veterans and to comment fairly on the work of others.

Had reviewers studied our fifth paper, they would have learned that failure to query veterans concerning their combat experience is widespread in VA facilities. Dr. Hobson's attitude is consistent with these practices.

Exposure Method:

We are heavily criticized for using the veterans' own accounts of where they were during their service in Vietnam as part of our exposure classification. We acknowledge that independent data on troop movement could have made our job of exposure classification easier and *had the CDC made known and available its extensive holdings of data on troop movement earlier* we would certainly have used such data.

We wish to emphasize that where veterans have been randomly misclassified, effects on health outcomes must have been underestimated because random misclassification tends to drive associations toward the null. **That is, misclassification will make potential effects disappear, not create them from nothingness.**

In any case, we consider that our exposure measure is reasonable and produces reasonable results. The crux of the CDC argument about why it is unreasonable is that it does not 'agree' with their purported validation study. We, and many other reputable scientists, have never agreed that the study of blood collected some 20 years post exposure is the criterion by which all other methods are to be judged.

Uniformly, the reviewers adhere to the position articulated in the CDC's 'validation' paper, namely, that no exposure index based on military records, let alone ours, is valid or usable. If they truly believe this, then the CDC must perforce retract its birth defects study, which is based on two such indexes, and the Air Force should retract the Ranch Hand Study, which is based on an exceptionally crude index obtained by dividing the number of gallons of herbicide sprayed in a year by the number of Air Force personnel present in Vietnam during that year.

The Value of Internal Comparisons:

We do not wish to appear to be saying that our questionnaire is without fault, nor that our study design is beyond criticism. In fact, we point out and are well-aware of the limitations in generalizing from a cross-sectional survey. We are also aware that the exposures and the outcomes, because they are based on self-reports, will contain inherent variability and unreliability (as will, incidentally 'objective' measures). That is why we carefully constructed a study design that largely depends on internal comparison groups: Southeast Asia veterans to non-Southeast Asia veterans, and different levels of combat and herbicide exposure among those who served in Southeast Asia. Such design minimizes the possible systematic errors that were the concern of so many reviewers. Feinleib notes our use of internal comparisons.

Recall Bias:

Many reviewers (e.g., Sweeney) insisted that our results were irretrievably tainted by "recall bias," that is, by the presumably higher reporting of adverse health events by men who had higher exposure or combat scores. This cannot possibly account for the extraordinarily powerful and linear dose-response curves, or for the fact that these dose-responses were observed for some outcomes (in fact, those hypothesized to be related to exposure) and not others. In the case of herbicide exposure, no subjects could possibly have known at the time they filled out the questionnaire what their exposure score would be, so that recall bias of herbicide-related associations is simply an impossibility. (Dr. Worth, among others, makes this error.) **The unpleasant truth is that some of the reviewers use the term 'recall bias' as a polite euphemism for lying on the part of veterans.**

A Small Sample of Unsubstantiated Statistics, Glaring Errors, and Sloppy Reviewing:

We are particularly disheartened by the sloppiness shown in many of the reviews and we provide some examples of misreadings, misstatements and misinterpretations below. We would have hoped that reviewers charged with commenting on one of the few independent studies of Vietnam Veterans that is available, might have at least taken the trouble to read and report the numbers correctly and to seek assistance in understanding a simple random sampling method. They could even have gone so far as to follow customary scientific practice and common courtesy and contact one of the investigators if they had a question. The fact that this was not done is to us further evidence that the reviewers never intended to carry out a fair and impartial review but were on a 'hatchet' job mission.

Feinleib classifies the study as retrospective when it is cross-sectional. He confuses and misstates the denominators for combat exposed and herbicide exposed and then criticizes the study for inconsistent data. He mentions 'recall bias', yet fails to note that many of CDC's own VES findings mirrored ours, and fails to note the dose-response relationships and the consistent results presented throughout the five papers.

William H. Wolfe, Col., USAF, MC, asks, "Do Vietnam vets join the Legion in different patterns than non-Vietnam vets? This issue is not addressed and could cause severe bias." **The Colonel has simply not read the papers carefully.** The answer to his question is on p. 126 in Table 6. His characterization as "inappropriate" our use of Legion VA field service representatives in developing the VA study questions is incomprehensible; it would have been inexcusable *not* to use them. No one knows the VA's strengths and weaknesses better than these people. To ignore their knowledge and advice would be tantamount to conducting a study in an unfamiliar area of science without even doing a literature review. He alleges that we did not adequately review the literature but cites not a single relevant arti-

cle we missed. In fact, our Health Effects paper contains 68 references, including many CDC and Air Force studies, while the CDC's paper contains only 46.

Marie H. Sweeney, NIOSH, characterizes this as a "largely negative study." Our study may be many things, but it is not negative. This assertion is all the more surprising since she admits that "The results of this study implicate combat intensity as a contributor to increased social dysfunctioning."

Thomas R. O'Brien, Medical Epidemiologist, CDC, states that "the odds ratio is increased for almost all outcomes." In fact, of 57 outcomes presented in Tables 1-4 of paper 3, 23 were elevated. Of five reproductive outcomes studied, four were *unrelated* to herbicide exposure.

Lawrence Hobson, MD, Director of VA Environmental Medicine Office refers to the "trivial nature of the health effects attributed to exposure to Agent Orange." We wonder whether it is official VA policy that miscarriages are "trivial."

Donald G. Barnes, US EPA wished that our claim that herbicide handlers were probably exposed to herbicides were "supported by specific references to the literature." The health effects paper did in fact refer to two environmental exposure studies by Lavy and one by Kolmodin-Hedman (p. 170). He states that "combat followed AO spraying by several weeks." Our analysis of the CDC's battalion tapes, which recently became available, demonstrates numerous instances of direct exposure of troops.

Barnes also chides us for our conclusion that mere presence in Vietnam cannot be used as a proxy for exposure to AO, and says "that possibility was never seriously suggested by anyone." Barnes is mistaken. It is a premise seriously entertained by Han Kang (one of the VA reviewers) in his soft-tissue sarcoma study, by Lawrence in the New York State veteran cancer study, by Breslin in the VA proportionate mortality study, and in some Australian studies as well.

Karon's question about whether the study had sufficient statistical power is irrelevant: statistical power is moot once significant results are obtained.

DEPARTMENT OF THE AIR FORCE

PRESENTATION TO THE COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
UNITED STATES HOUSE OF REPRESENTATIVES

SUBJECT: Air Force Health Study July 10, 1989

STATEMENT OF: Colonel (Dr.) William H. Wolfe, USAF, MC
Principal Investigator
Air Force Health Study

NOT FOR PUBLICATION UNTIL RELEASED
BY THE COMMITTEE ON VETERANS' AFFAIRS,
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
UNITED STATES HOUSE OF REPRESENTATIVES

Colonel (Dr.) William H. Wolfe

Colonel (Dr.) William H. Wolfe is the chief of the Epidemiology Division, U.S. Air Force School of Aerospace Medicine, Human Systems Division, Brooks AFB, Texas. In this position, he directs the sole U.S. Air Force laboratory providing worldwide epidemiologic support and diagnostic and referral laboratory service. He is also the principal investigator for the Air Force Health Study, a 20-year epidemiologic investigation of the possible adverse health effects from herbicide exposure.

Colonel Wolfe was born December 4, 1943, in Baltimore, MD. He graduated from Washington & Lee High School, Arlington, VA in 1961. He earned a bachelor of science degree in biology in 1965 from the College of William and Mary, Williamsburg, VA. In 1969, he was awarded his doctorate in medicine from the Medical College of Virginia, Richmond and completed an internship in 1970 at the Medical College of Georgia in Augusta. Colonel Wolfe also earned a master's degree in public health (epidemiology) from the University of Washington School of Public Health and Community Medicine, Seattle, in 1977. He completed his general preventive medicine residency at Brooks in 1978.

Colonel Wolfe received his commission in 1970. He has served as a general medical officer at Perrin AFB, TX and at Hancock Field, NY. He later served as squadron flight surgeon from the 53rd Tactical Fighter Squadron, Bitburg Air Base, Germany. At Iraklion Air Station, Crete, he was the chief of professional services and director of base medical services. After completing his preventive medicine residency at the U.S. Air Force School of Aerospace Medicine in 1978, he continued his affiliation with the School as the chief, Disease Surveillance Branch Epidemiology Division and as chief, Epidemiology Services Branch. He assumed his present position in 1984.

Colonel Wolfe's military decorations include the Humanitarian Service Medal, the Air Force Commendation Medal, the Joint Service Commendation Medal and the Air Force Meritorious Service Medal. Additionally, he is the recipient of the U.S. Air Force Scientific Achievement Award and the William Gorgas Medal, the highest award given to a federal employee for distinguished work in the field of preventive medicine.

The colonel's professional affiliations include the Aerospace Medical Association, the American College of Preventive Medicine, and the Association of Military Surgeons of the United States. His appointments include consultant to the U.S. Air Force Surgeon General in preventive medicine, consultant to the Department of Veteran's Affairs on medical effects of phenoxy herbicides, consultant to the government of Australia on Human Health Effects of Phenoxy Herbicides and Dioxins (1981) and member, Agent Orange Working Group Science Panel (1987-1989).

In 1978, the United States Air Force, responding to Congressional and veterans' interest in the controversial issue of Herbicide Orange exposure and health effects, began work on an epidemiologic study of the possible health effects of exposure to herbicides and their 2,3,7,8-tetrachloridobenzo-p-dioxin (referred to as dioxin or TCDD) contaminants. Our study focused on Air Force veterans who served in the Ranch Hand defoliation operation during the Vietnam conflict.

The study was based on a scientific approach. We developed a protocol for a study including all 1267 members of the Ranch Hand unit serving from 1962 to 1971 and a group of matched comparisons. The comparison group was selected from the population of Air Force veterans who served in C-130 aircraft units stationed in Southeast Asia during the same time period. They were matched to the Ranch Hand group by age, race and job (pilot, navigator, non-flying officer, flying enlisted, and ground enlisted). It was assumed the comparisons were not exposed to herbicides or dioxin in Southeast Asia.

The protocol was subjected to extensive review by scientific peer groups including the University of Texas School of Public Health, the Air Force Scientific Advisory Board, the Armed Forces Epidemiological Board, the National Academy of Science, and the Science Panel of the Agent Orange Working Group.

The protocol was approved in February 1981 and the first questionnaires were administered in October of that year. Nearly 2,300 men were given physical examinations in 1982, 1985, and 1987. Other examinations are scheduled for 1992, 1997, and 2002. The results of the 1982 physical examination were published in 1984; the 1985 physical exam results were published in 1987 and the results of the 1987 exam should be published in early 1990. The study focuses on three primary areas: current and past illness, the death experience of the two groups, and birth defects in children fathered by the study participants. Our study is a planned 20 year research effort. To date, we have published five mortality reports and two morbidity reports.

A comprehensive clinical evaluation has been and will be performed throughout the study with examinations by internal medicine, neurology, and dermatology specialists. Psychological and laboratory testing has been and will be included.

Participation in the study has been excellent with 87 percent of the invited Ranch Hands and 75 percent of the invited comparisons taking part in the initial evaluation; 93 percent of those who participated in the initial study have returned for the follow-up examinations.

The results of the 1985 data were released in October 1987. It was found that the objectively measurable health of the exposed men was generally equivalent to that of the unexposed group. Physician examiners detected no differences for appearance of

illness or distress or for the appearance of relative age. The Ranch Hands had significantly lower percent body fat. They also had a higher proportion of sedimentation rate abnormalities than the comparisons, but mean sedimentation rates were not statistically different between the two groups.

Despite these facts, in terms of perceived health, Ranch Hand enlisted groundcrew rated their health as fair or poor more frequently than their comparison group; similar perceptions were not observed for the enlisted flyers or the officers.

The study has limited power to detect group differences in specific types of cancer since only 1,267 where assigned to the Ranch Hand units, therefore the study focused on systemic and skin cancer as broad categories of disease. No significant differences between the Ranch Hand and the comparison groups were seen in the 1987 report for systemic cancers. However, skin cancer was an exception. When overall lifetime basal cell carcinoma rates were adjusted for causative risk factors (e.g., geographic area of residence, skin color, skin reaction to the sun) Ranch Hands had a statistically significant higher number of basal cell carcinomas than the comparisons. These basal cell cancers were found in sun exposed areas of the body in Caucasian patients exclusively. This basal cell is the most common neoplasm in the white population in the United States, is not prone to distant spread, and is amenable to complete cure. This trend which was first detected in the

initial physical examination was not as significant in the follow-up exam.

The 1987 report cited an apparent increase in systemic cancer among enlisted flyers. However, no significant group differences in life-time systemic cancer were found on reanalysis of the data after review of additional medical records and correction of coding errors. Two cases of possible dioxin related cancer (soft-tissue sarcoma and non-Hodgkins lymphoma) in Ranch Hands were suspected at the time of the 1987 report; these have since been confirmed, bringing the life-time total to two of these cancers in both Ranch Hand and control groups.

The neurologic assessment of cranial nerve function, peripheral nerve function, and central nervous system coordination did not reveal any consistently significant group differences in the 1987 report. The Babinski reflex (found abnormal in a higher number of Ranch Hands at the 1982 Baseline examination) was likewise not significantly different from controls at follow-up. Age, alcohol, and diabetes showed expected effects on several neurological parameters in both groups.

Extensive psychological testing was conducted. In general, while statistically significant differences in some portions of the testing were seen, they were quite variable in nature and their clinical relevance is unknown. Post traumatic stress disorder was evaluated, and only 1 percent in either group had

this condition. There were no group differences for current or past neuroses or psychoses. Age, educational level, and alcohol history showed strong and expected effects on the psychological measures in both groups.

Both the interval and lifetime history of liver disease were comparable in both groups, as was a lifetime history of peptic ulcer disease in the 1987 report. Of the 11 laboratory tests performed to evaluate liver function, two showed significant group differences in the average values. However, the number of men who had abnormally high levels was not significantly different in the two groups. The uroporphyrin test, which is the best indicator of porphyria cutanea tarda, a condition at one time thought possibly related to dioxin exposure, was normal in the Ranch Hands. This test was significantly elevated in the control group.

In the dermatological examination by specialists, no case of chloracne was diagnosed. Nor was the history of prior acne distributed in an anatomic pattern that suggested past chloracne. Exposure index analyses and comparison with the results of the 1984 report were also unremarkable.

The 1987 report found an apparent increase of verified heart disease in the Ranch Hand group. This observation was no longer seen on reanalysis of the data after review of additional medical

records. There were no group differences for hypertension or heart attacks.

In the 1985 physical examination, peripheral pulses were examined by Doppler technique and neither group had unusual pulse deficits. At this examination, the effect of tobacco was controlled by restricting smoking for four hours prior to the measurement of the pulses. Overall, the groups were remarkably similar in cardiovascular health, and no statistical differences were found.

The 1985 assessment of eight hematological measures continued to show no significant group differences. Age, race, and smoking were significant risk factors for most hematological parameters in both groups.

The groups did not differ significantly in reported kidney disease in the 1987 report, although previous data noted such in the Ranch Hands. Five laboratory measures of actual renal function were quite similar between groups in relation to known elements of risk.

Overall, the endocrine health status was comparable in both groups. As measures of endocrine function, TSH and testosterone levels were significantly higher in the Ranch Hands but still within the normal range. Abnormal glucose tolerance tests were significantly higher in the comparison group. Additional tests

for cortisol level and T3 percent uptake, were similar in both groups. Physical examinations for thyroid and testicular abnormalities were comparable in both groups. Age, race, occupation, percent body fat, and personality type were taken into account as pertinent variables.

Comprehensive immunological tests, composed of six cell surface marker studies and three functional stimulation studies showed no significant group differences. Age, smoking, and alcohol usage were accounted for in the analysis. The data on delayed hypersensitivity by skin testings were uninterpretable because of lack of reproducibility due to reader variation.

The pulmonary assessment, in the 1987 report, consisting of past history, physical examination, and x-ray results did not indicate any consistently different disease patterns in the two groups. Age and lifetime smoking history were important risk factors for both groups.

The exposure index analyses, revealed no consistent dose-response relationships that supported a herbicide effect in any clinical area.

A comparison between the findings of the 1982 and the 1985 studies involving 19 variables showed five significant differences over time. One of these, sedimentation rate, was believed to be related to a change in laboratory methods. The

other four (Babinski reflex, depression, platelet count, and manual pulse index) were attributed to real changes primarily in the Ranch Hands over time. These changes brought the two groups into even closer alignment over the three year period.

By direct and indirect means, we have insured that this study is free of overt bias and that the measurement systems used to obtain the data were valid and accurate. We have concluded that the few variations between the Ranch Hand and control groups are not supportive of a hypothesis of adverse health in the Ranch Hands to date. The study has revealed a number of minor differences that require continued surveillance. In full context, this study offers encouraging evidence that, the current state of health of the Ranch Hand participants appears unrelated to herbicide exposure in Southeast Asia. We emphasize that it is nevertheless premature to fully exonerate the herbicide in terms of morbidity at this time.

In addition to the morbidity analyses, we have conducted periodic evaluations of the death (mortality) experience of the Ranch Hand and comparison groups and reported on them. Analyses have been directed at total and cause-specific death rates with adjustment for year of birth, race, military rank, and occupation. The reports have repeatedly demonstrated similar death experience in the two groups, with no apparent effect from Herbicide Orange exposure. The latest analysis includes the death experience of approximately 20,000 men (all of the Ranch Hands and all men

assigned to C-130 aircraft units in Southeast Asia between 1962 and 1971).

This latest evaluation differs from previous statistical contrasts of Ranch Hand and comparison mortality in that for the first time we have been able to take the mortality experience of the entire comparison population as the standard against which Ranch Hand mortality has been compared.

The indirectly standardized Ranch Hand mortality rate for all causes of death is 2.5 deaths per 1000 person-years and the corresponding rates for the matched comparisons and the entire comparison population are 3.0 and 2.5 deaths per 1000 person-years respectively. The overall adjusted relative risks assessing Ranch Hand mortality with all comparisons is 1.0.

Digestive system deaths were significantly more frequent in Ranch Hands. However, six Ranch Hand digestive system deaths were attributed to alcohol consumption. Thus the variation was apparently unrelated to herbicide exposure.

An increasing trend in post-1983 death rates among Ranch Hand flying officers was noted in the latest mortality analysis. This appeared due to malignant neoplasm deaths. In previous reports, this group of officers had lower mortality than their comparisons. Now the officer groups appear to be equivalent. Ranch Hand malignant neoplasm deaths in the flying officers are not

restricted to a particular anatomic site or cancer type as would be expected if Herbicide Orange and its dioxin contaminant were exerting a direct effect on malignant disease. It is not known whether this difference represents a statistical catch-up or a continuing trend.

In conclusion, the overall cumulative mortality of the Ranch Hands to date remains statistically indistinguishable from that of both the matched group and total comparison population. Ranch Hands are similar to all comparisons in cumulative accidental, malignant neoplasm, and circulatory system mortality. Nevertheless, as in the morbidity studies, it is premature to make a final judgment. The study design calls for mortality to be compiled for another 12 years.

There has been much controversy concerning the relationship between herbicide exposure and birth defects in children. Initial evaluation of fertility and reproductive systems found that there was significant disparity between groups for reported birth defects. We incorrectly concluded that group differences were confined to minor skin conditions. Preliminary baseline findings suggesting adverse group differences in Ranch Hand progeny is being reinvestigated using direct medical record verification of the reported birth defects. For the 6,723 children fathered by study participants the rate of missing records, 1.3 percent is exceptionally low. This will strengthen statistical analysis which

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we anticipate will be ready for the Advisory Committee by early next year.

We have made some effort to place our data in context with other scientific findings. Most large scale studies of veterans dealt with the effects of general service in Vietnam and did not directly address exposure to herbicide orange and its dioxin contaminant. The Centers for Disease Control's (CDC) Vietnam Experience Study (VES) of 2,490 Vietnam and 1,972 non-Vietnam veterans found that Vietnam veterans reported somatic symptoms and physician verified diseases more frequently than did non-Vietnam veterans. Most of these reported conditions were not detected during the physical examinations. We likewise found evidence of increased somatic symptoms in Ranch Hands, but there were few detectable group differences by physical examination or laboratory data.

Vietnam veterans in the VES were found to have a greater degree of hearing loss than the non-Vietnam veterans, especially among those who served in tactical military settings. Our hearing loss data is currently being analyzed and results will not be available until early in 1990. Among a subsample of VES participants who had semen samples evaluated, more Vietnam veterans had decreased sperm concentrations and a smaller proportion of normal sperm cells than the non-Vietnam group, although both groups fathered a similar number of children. We

found no group differences in sperm abnormalities among the subsample of our study who had semen studies done in 1982.

Many studies of Vietnam veterans assume that mere presence in Vietnam equaled dioxin exposure. Mounting evidence invalidates this assumption. Dioxin studies in veterans done by Massachusetts, New Jersey and the CDC are very comparable to our data: men whose military duties in Vietnam involved direct and repetitive handling of herbicides harbor increased serum dioxin levels, while men involved in other duties (infantrymen and C-130 aircraft crews and support personnel) have levels at or below normal background.

Exposure Index

Early phases of our studies, as those of other investigators, were hampered by absence of a verifiable method to directly assess a person's dioxin level. To circumvent this difficulty, our initial study protocol included an estimated exposure index which reflected a calculation of the effective exposure of our airmen to dioxin. It is based on total gallons of herbicide sprayed per month (1962-1971), levels of dioxin contaminant per gallon, and the number of men assigned to each occupation each month.

Now that direct measurement of serum dioxin levels is feasable, it is clear that the "estimated exposure index" while a reasonable approach, did not accurately predict exposure for any individual. When assay data are available on our participants,

the original exposure index will be discarded. Based on paired samples of 36 study participants, dioxin half-life has been shown to be 7.1 years in a collaborative study between the Air Force and the CDC.

Serum has been collected and stored from 1,999 study participants. To date, assay results on 1,005 of these have been received from the CDC, and the remaining specimens should be completed by the end of January 1990. The results, (see attached table) demonstrate that the enlisted Air Force ground personnel as a group have the highest levels of dioxin. Officers had the least.

The ability to move from estimates to direct measurement of Herbicide Orange exposure for study participants has eliminated the need to make assumptions about the level of individual exposure. This will significantly improve the scientific accuracy of the study.

Dioxin Assay Results

Stratum	Ranch Hand N	Ranch Hand Median	Ranch Hand Range	Comparisons N	Comparisons Median	Comparisons Range
Pilots	157	7	0-42	94	5	2-13
Navigators	39	9	1-36	22	5	2-8
Adm Officer	14	7	3-25	3	4	4-5
Flight Eng	98	16	1-127	68	4	1-13
Ground Crew	312	23	0-313	198	4	0-27

STATEMENT OF
CONGRESSMAN CLIFF
STEARNS

JULY 10, 1988

Thank you Mr. Chairman for your consideration in allowing all members of this committee to sit in on this important hearing on one of the most controversial issues we will deal with this year, Agent Orange.

During the Vietnam war, thousands of military men and women were exposed to an herbicide called Agent Orange, an exfoliant which has a base of dioxin, a cancer-causing substance. Since that time, concerned organizations representing these veterans have asked Congress to study the health effects of their exposure to Agent Orange.

Several studies have been done, and we will hear testimony on the results of those studies today. I am

looking forward to learning more about the findings of these studies, and the opinions of the witnesses on the need for further study and possible Congressional action to make sure that the needs of these veterans are discovered and dealt with as soon as possible. If, in fact, veterans' exposure to Agent Orange in the performance of their duty to this country has put them at risk for certain diseases, and that link can be proven with some measure of certainty, it is our duty to see that they are given proper care and compensation.

I look forward to hearing from ~~you~~ OUR PANEL today on this important issue.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

SUICIDE AMONG VIETNAM VETERANS

The media have reported that suicides among Vietnam veterans range from 50,000 to over 100,000. In 1981, the figure of 50,000 was widely used. Then in 1986 and 1987, two books were published that suggested there were more than 60,000 suicides among Vietnam veterans. In October 1987, a lecturer in a history course on war appeared on a popular Sunday evening television program and stated that there were more than 100,000 suicides in Vietnam veterans. Mortality studies show that 9,000 is a better estimate.

Suicide among Vietnam veterans first emerged as a prominent national issue during the late 1970's. In October 1978, a Presidential Review Memorandum on Vietnam Era Veterans, which was provided to Congress, included the statement that Vietnam era veterans less than 34 years old had been found to have a suicide rate 23 percent higher than nonveterans. Subsequently, it was discovered that this reported excess of suicides was based on a study conducted in a Veterans Administration (VA) Hospital in which hospitalized Vietnam era veterans were compared with older hospitalized patients. In early 1979, in response to a congressional inquiry, the statement regarding excess suicides was retracted by the Administrator of Veterans Affairs. In a letter to the Chairman of the House Committee on Veterans' Affairs, the Administrator wrote "There are no published statistics on rates of suicide among nonhospitalized Vietnam era veterans and hence no precise statement can be made regarding such rates relative to those for the general population matched for sex and age."

Evidently, this commentary on the suicide data was not widely disseminated. A VA psychiatrist repeated the report of excess suicides with an article that appeared in the Journal of the American Medical Association in August 1981. The President's Memorandum also continued to receive attention in the popular press and in veterans' magazines but with a significant difference. The increased risk for suicides was described as occurring just among the approximately 2.6 million veterans of the Vietnam conflict rather than among the more than 8 million veterans who served during the Vietnam era. Furthermore, the increased risk was described as occurring among Vietnam veterans of all ages.

The CDC Vietnam Experience Study Mortality Assessment showed that during the first 5 years after discharge deaths from suicide were 1.7 times more likely among Vietnam veterans than non-Vietnam veterans. After that initial postservice period, Vietnam veterans were no more likely to die from suicide than non-Vietnam veterans. In fact, after the 5-year postservice period, the rate of suicides is less in the Vietnam veterans group.

Of the several mortality studies of Vietnam veterans, only the CDC study and the Wisconsin Department of Health Vietnam Veterans Study provide suicide rates necessary to estimate the number of suicides among all Vietnam veterans. Using either study, the projected number is approximately 9,000 (95% CI=6, 500-13,000) suicides expected among the 2.6 million veterans of the Vietnam conflict.

The proportion of deaths due to suicide in CDC's investigation (13%) is comparable with the proportions found in four State mortality studies (9%-16%)--Wisconsin, Massachusetts, New York, and West Virginia.

At any time during the Vietnam conflict, 37 million males in the United States were aged 18 through 35. Vital statistics show that the total number of suicides in this population of 37 million males through 1985 was slightly under 152,000. Of these 37 million males, 2.6 million served in Vietnam. If the reports in the press of up to 100,000 suicides were accurate, this would indicate that two-thirds of all the suicides that occurred in this population of 37 million men came from the 2.6 million who served in Vietnam. This is not supported by any factual information.

We are submitting an abstract of a CDC presentation entitled "Estimating the Number of Suicides Among Vietnam Veterans" for the record. This abstract was presented at the 1988 meeting of the Society of Epidemiologic Research in Vancouver, British Columbia, Canada.

were identified for whom blood had been drawn and stored an average of 62.9 months before a pathologic diagnosis of non-Hodgkin's lymphoma was made. From the same populations, 245 controls matched for race, sex, age, and date of index serum collection were obtained. Conditional logistic regression analysis revealed that increased risk of non-Hodgkin's lymphoma was associated with elevated anti-VCA immunoglobulin G (odds ratio = 2.1 (95% confidence interval = 0.9–4.9), and anti-VCA immunoglobulin G (2.35 (0.9–6.4)). There was no apparent association with antibody against early antigen: early restricted antigen, 1.2 (0.5–3.2), early diffuse antigen, 1.1 (0.4–3.0), and lack of response for nuclear antigen, 0.4 (0.2–1.2). These findings suggest that chronic Epstein-Barr virus replication occurs years before diagnosis, and support the role of Epstein-Barr virus either in the pathogenesis of non-Hodgkin's lymphoma or as an important marker of immune function.

Estimating the number of suicides among Vietnam veterans. D. Pollock,* P. Rhodes, and C. Boyle (CDC, Atlanta, GA 30333).

In the mid-1980s, the US news media reported that more than 50,000 Vietnam veterans had committed suicide since discharge from service. Despite wide dissemination of this alarming statistic, the total number of Vietnam veteran suicides has not been estimated from the scientifically-based follow-up studies of veterans conducted at the state and national levels. The authors use data from the Centers for Disease Control's US Army Vietnam Experience Study to estimate the cumulative number of Vietnam veteran suicides through December 31, 1983. In this study, the vital status of 9,324 Vietnam veterans was ascertained. There were 246 deaths, including 29 suicides by death certificate in the Vietnam veteran cohort; a medical review of all available supplementary cause-of-death records resulted in an increase in the number of suicides to 33. The proportion of deaths due to suicide in this investigation (0.13) is comparable with the proportions found in four state level mortality studies (0.09 to 0.16). Projecting the present results to the approximately 2,600,000 military personnel who served in Vietnam leads to an estimate of 9,200 suicides through 1983 (95% confidence interval = 6,550–12,950). This finding is further evaluated using national vital statistics for age-specific suicide rates for 1968–1985. The authors conclude that the number of Vietnam veteran suicides reported in the news media is a marked overestimate.

ABRAHAM M. LILIENFELD STUDENT PRIZE PAPER

Spontaneous abortions in relation to water consumption: an application of survival analysis to studies of pregnancy loss. I. Hertz-Picciotto* (California Dept. of Health Services, Berkeley, CA 94704), S. Swan, R. Neutra, and S. J. Samuels.

A previous study of pregnant women whose water supply was potentially contaminated revealed a significant increase in spontaneous abortions among women who drank tap water compared with women who drank bottled water, regardless of exposure status. The relation between water consumption and risk of spontaneous abortion was therefore analyzed in an independent cohort of pregnancies from a health maintenance organization in the same region. A nested case-control study compared livebirths with spontaneous abortions; the crude odds ratio for tap vs. bottled water was 1.7 (95% confidence interval (CI) = 1.2–2.3). Because early spontaneous abortions are left-truncated, gestational age at which a pregnancy comes to medical attention may confound results of studies of fetal loss. In this study, age-at-entry varied by geographic area, as did crude risks of spontaneous abortions. With the use of the sampling fractions of the nested design, a risk set analysis was conducted in two stages: 1) stratified lifetable-adjusted risks were determined for women who drank mainly tap water (16%) or mainly bottled water (9%); 2) the Cox model was used to control for multiple confounders, yielding a hazard ratio for tap water vs. bottled water of 1.5 (95% CI = 1.1–2.0). Women who received ground water were at higher risk than those who received pure surface water. Compared with published lifetable risks of spontaneous abortion, the risk for bottled water drinkers may be unusually low. Recall bias is strongly suggested by other evidence in this data set, although a causal relation has not been ruled out.

INVITED ADDRESS

Epidemiology, politics, and policy. M. A. Ibrahim* (School of Public Health, U. of North Carolina, Chapel Hill, NC 27514).

Policy is viewed from a set of perspectives with complex interrelations. In addition to the scientific/epidemiologic evidence, concerns of government, industry, population, scientific and popular media, and international community, among others, come into play to impact on making health policy. The potential harmful and beneficial relation of aspirin to Reye's syndrome and myocardial infarction, respectively, is a case in point. Exposure to aspirin among children with influenza or chickenpox has been linked to the development of Reye's syndrome. Warning labels (that can't be read easily even with reading glasses) were posted on aspirin bottles on a temporary basis, but, in view of the current evidence, such labels will remain in effect for the foreseeable future. The protective role of aspirin in primary and secondary prevention of myocardial infarction has led to overly optimistic claims by the industry. The US Food and Drug Administration issued an advisory for the industry to moderate its claims but did not require withdrawal of the ads. The scientific and popular media played an important part in the dissemination of the findings. Another case example is illustrated by the relation between smoking and ill health. In spite of the conclusive evidence about smoking and illness, political and economic considerations have blunted efforts to ban smoking. When governments derive substantial revenue from tobacco, efforts to ban smoking in public places and workplaces become more difficult to implement. Efforts to reduce red meat consumption are similarly hampered when governments depend on the beef industry for revenue. The contribution of epidemiology to understanding the causes of disease and consequently the formulation of policy for improving health states of populations are crucial in addressing contemporary health issues.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

Deaths Due to External Causes
Among Vietnam and Non-Vietnam
Veterans (1965-1983)

The following table, taken from the CDC monograph Postservice Mortality Among Vietnam Veterans, shows the number of deaths from external causes by specific cause and time since discharge. As indicated in Table 23 of the monograph:

> Deaths due to MVAs are significantly elevated among Vietnam veterans in the first five years after discharge (RR=1.93). After 5 years, the excess is considerably less, although still somewhat elevated (RR=1.16). No association is seen in either time period for accidental deaths other than those from motor vehicles or poisonings.
>
> For deaths due to suicide, a 72% nonsignificant increase is seen among Vietnam veterans in the initial 5 years of follow-up, but a deficit is seen thereafter. Because of possible inaccuracy in the recording of suicide on death certificates, we broadened the definition to include all accidental poisonings (E850-E989), and ill-defined and unknown causes of death (799.9). The main difference between the results of this new category and the previous one is the slight, nonsignificant elevation in risk now seen in the later follow-up period. (RR=1.12). Finally, an early postservice excess is seen for deaths due to homicide but the relative risk drops below 1.0 thereafter. There were no postservice deaths due to war-related injuries.

Table 23. Numbers of Deaths From External Causes (from Death Certificate) Among Vietnam and Non-Vietnam Veterans Combined and Unadjusted Rate Ratios, by Specific Cause and Time Since Discharge (1965-1983)

External cause	Years since discharge*					
	<5 years			6+ years		
	No. deaths	Rate ratio	95% CI	No. deaths	Rate ratio	95% CI
Motor vehicle accident	66	1.93	1.16-3.22	67	1.16	0.72-1.87
Other accidents+	23	1.05	0.46-2.39	39	0.89	0.48-1.67
Suicide	25	1.72	0.76-3.88	32	0.64	0.32-1.30
Suicide++	39	1.72	0.90-3.32	46	1 12	0.63-2.00
Homicide	18	1.52	0.59-3.91	33	0.78	0.39-1.55

*Number of deaths and RRs for "all years" of follow-up are presented in Table 22.
+Includes accidental deaths other than motor vehicle accidents and accidental poisonings.
++Includes: accidental poisonings (E850-869), suicides (E950-959) injury undetermined whether accidentally or purposefully inflicted (E980-989) and ill-defined or unknown cause of death (799.9).

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Congress of the United States
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WASHINGTON, DC 20510-8025

January 26, 1989

The Honorable G.V. Montgomery
Chairman
Committee on Veterans' Affairs
U. S. House of Representatives
Washington, D.C. 20515

Dear Sonny:

The enclosed OTA Staff Paper reviews a study titled "The Columbia University-American Legion Vietnam Veterans Study" sponsored by the American Legion of the effects of service in Southeast Asia during the Vietnam era. As you and your colleagues requested in your letter of November 22, 1988, the OTA review discusses the scientific methods used and the validity of the findings.

The study (referred to as "The American Legion Study") is based on responses to a mailed questionnaire by a sample of Legionnaires in six states who had served either in Southeast Asia (SEA) or elsewhere during the Vietnam era. Questions concerning military experiences and aspects of subsequent functioning and wellbeing were asked. The study was conducted by researchers based at the Columbia University School of Public Health, and the results were published in five papers in the December 1988 issue of Environmental Research.

The study investigators reported deficits in a number of social, economic, physical, and psychological measures that they attributed to having served in SEA. They also reported that among SEA veterans, problems appeared to be associated with the extent of combat experience and with having higher scores on an Agent Orange exposure estimate scale.

OTA finds that the study has major flaws that call into question the validity of virtually all the findings reported. These flaws include: 1) aspects of the method of selecting the study population and low rate of response to the questionnaire, both of which may have contributed to a biased comparison of SEA and non-SEA veterans, and of subgroups of SEA veterans; 2) an unvalidated and probably invalid method for assessing Agent Orange exposure; and 3) an unvalidated and probably invalid approach to collecting health (and possibly other) information about the participants. All epidemiologic studies suffer from some bias, and no methodology is perfect. However, the American Legion study has such serious problems that, even though some of its conclusions might be correct, the evidence produced by the study cannot be relied upon for an understanding of the consequences of having served in SEA during the Vietnam era.

An editorial by Michael Gochfeld, which accompanies the American Legion Study reports, suggests that the method used to estimate exposure to Agent Orange in this study is an improvement on previous attempts, and should be applied widely in other studies of veterans. He ascribes the Government's decision to halt the Congressionally-mandated Agent Orange study to CDC's "arguing nihilistically that since exposure cannot be well documented, the study was not feasible." The Government's decision was made because of compelling evidence, from serum dioxin testing and also from a more sophisticated exposure estimation procedure than that used by the American Legion investigators, that there did not exist a large group of ground troops with significant exposure. The American Legion Study has done nothing to alter these conclusions.

I hope you find this review helpful. If you have any questions or comments on it, please feel free to call me, or to contact Clyde Behney or Hellen Gelband of the OTA Health Program (at 8-6590).

Sincerely,

John H. Gibbons

enclosure

OTA Review of:

The Columbia University-American Legion Vietnam Veterans Study

Staff Paper
Prepared by Hellen Gelband

Special Projects Office of the Health Program

Office of Technology Assessment
U.S. Congress

January 1989

The views expressed in this Staff Paper do not necessarily represent the views of the Technology Assessment Board or its individual members.

OTA Review of:

THE COLUMBIA UNIVERSITY-AMERICAN LEGION VIETNAM VETERANS STUDY

SUMMARY

The American Legion sponsored a study in which a sample of their membership who had served during the Vietnam era filled out questionnaires concerning their military experiences and aspects of their subsequent functioning and wellbeing. The study was conducted by researchers based at the Columbia University School of Public Health, and the results were published in five papers published in the December 1988 issue of Environmental Research.

The investigators reported deficits in a number of social, economic, physical, and psychological measures that they related to having served in Southeast Asia (SEA). They also reported that among SEA veterans, problems appeared to be associated with more extensive reported combat experience, and with having higher scores on an Agent Orange exposure estimate scale. OTA was asked by the Chairmen and Ranking Minority Members of the Senate and House of Representatives Committees on Veterans' Affairs to comment on the methodology of the Columbia University-American Legion Vietnam Veterans Study (referred to as the "American Legion Study"), as well as the validity and strength of the findings reported.

This study has major flaws that call into question the validity of virtually all the findings reported. These flaws include: 1) aspects of the method of selecting the study population and low rate of response to the

questionnaire, both of which may have contributed to a biased comparison of SEA and non-SEA veterans, and of subgroups of SEA veterans; 2) an unvalidated and probably invalid method for assessing Agent Orange exposure; and 3) an unvalidated and probably invalid approach to collecting health (and possibly other) information about the participants. All epidemiologic studies suffer from some bias, and no methodology is perfect. However, the American Legion study has such serious problems that, even though some of its conclusions might be correct, the evidence produced by the study cannot be relied upon for an understanding of the consequences of having served in SEA during the Vietnam era.

Introduction

This review gives a general description of the design and findings of the American Legion study, and discusses the Agent Orange exposure estimation methodology used, aspects of the participant selection process that might have affected the results, problems with self-reported data of the type collected in this study, and problems with the study questionnaire. The review concentrates on reported physical and psychological health outcomes.

Description of the Study and Findings

The American Legion study is a cross-sectional survey of 2,858 veterans who served in Southeast Asia during the Vietnam era (SEA veterans) and 3,952 who served elsewhere during that time. These were the respondents out of 12,588 Vietnam-era veterans to whom questionnaires were mailed.[1] While the participants are described as a "random sample" in the reports, that does not appear to be the case, as explained below (see Study Population).

1. Stellman, Jeanne M., and Stellman, Steven D., "Columbia University--American Legion Vietnam veterans study: Report #1," booklet, dated May 29, 1985.

Respondents filled out a printed questionnaire[2] and sent it back to the investigators. The questions cover military experience, basic demographics and education, attitudes toward the Veterans Administration, personal health history and current status, reproductive history, some aspects of lifestyle, economic status, and social relationships. The questionnaires were the sole source of information for the analyses published in Environmental Research; no independent documentation (e.g., military or medical records) of any information was collected. (A statement is made, however, that data on birth defects will be presented in a future report because of the necessity for medical verification.) Some problems with the questionnaire are discussed below (see The Questionnaire).

A variety of standard statistical techniques were used in the analyses, but inconsistencies in the types of adjustments made caused difficulties in interpreting some results. For example, some analyses relating findings to Agent Orange exposure scores are adjusted to attempt to remove the effect of combat (the study's Agent Orange exposure scores and combat scores are highly correlated), but some are not, leaving a question as to whether effects seen are associated with Agent Orange scores, combat scores, or both. In general, not enough information is given for the reader to reproduce the analyses given or to reanalyze the data in other ways.

Despite a wealth of detail, the study methodology is not described sufficiently well, there appear to be inconsistencies throughout the papers in the numbers of men in various categories, and there is a general lack of precision in reporting the methods and findings.

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2. Vietnam Era Veterans Study, printed questionnaire, including letter signed by Keith Kreul and Jeanne M. Stellman, Ph.D., 12 pp., January 1984.

Reported Health and Reproductive Outcomes

Health and reproductive outcomes are discussed in one paper.[3] A variety of physical conditions were reported more frequently by SEA veterans than by non-SEA veterans. These include: heart disease, venereal disease, benign fatty tumors, and various skin conditions. A greater percentage of men who reported handling herbicides directly, compared with other men who served in SEA, reported higher rates of high blood pressure, heart disease (but not when adjusted for differing age distributions), stomach or duodenal ulcer, and various skin conditions. Among men who served in SEA but did not handle herbicides directly, higher rates of benign fatty tumors and various skin conditions are reported with higher Agent Orange exposure scores. Among SEA veterans (excluding those who handled herbicides directly), higher rates of a number of conditions were reported in association with higher combat exposure scores: high blood pressure, stomach or duodenal ulcer, benign fatty tumors, arthritis or rheumatism, hepatitis, genito-urinary problems, nervous system disease, and major injury. In another analysis, various symptoms were grouped into five scales called 1) faint, 2) fatigue, 3) aches, 4) colds, and 5) skin. On the questionnaire, men were given a choice among the following answers to rate the symptoms included in these scales: 1) not a problem, 2) minor problems, 3) a problem, or 4) really a major problem. Results reported are as follows: 1) SEA veterans scored significantly higher (more problem symptoms) than non-SEA veterans on each scale; 2) men who reported handling herbicides directly had significantly higher scores on each scale than did other SEA veterans; 3) in multiple regression analysis, combat scores and Agent Orange

3. Stellman, Steven D., Stellman, Jeanne Mager, and Sommer, John F., Jr., "Health and reproductive outcomes among American Legionnaires in relation to combat and herbicide exposure in Vietnam," Environmental Research 47:150-174, 1988.

exposure scores were correlated with scores on each scale. In the latter analyses, the combat scale was more strongly correlated than was the Agent Orange scale.

A slightly (but significantly) higher percentage of SEA veterans compared with non-SEA veterans reported either having children or having tried to have children (90.3 percent vs. 88.4 percent); the percentage increased significantly with combat level (low, medium, high). The percentage reporting difficulty having children was significantly higher among SEA veterans compared with non-SEA veterans (18.0 percent vs. 14.9 percent), but was not associated with combat levels. Rates of miscarriage in female partners correlated with Agent Orange exposure scores and with combat scores.

Post-traumatic Stress Disorder (PTSD)

Between 1.8 and 15.0 percent of SEA veterans in the study were reported to have PTSD, depending upon which of three definitions was used.[4] Using at least one of the definitions, the rate of PTSD increased with increasing combat scores.

Agent Orange Exposure Estimation Method

The method used to arrive at numeric Agent Orange (and other herbicide) exposure scores for individual participants is described in a 1986 paper by Stellman and Stellman.[5] As have previous attempts at developing an Agent Orange exposure index, this one combines information from soldiers' locations

4. Snow, Barry R., Stellman, Jeanne Mager, Stellman, Steven D., and Sommer, John F., Jr., "Post-traumatic stress disorder among American Legionnaires in relation to combat experience in Vietnam: Associated and contributing factors," Environmental Research 47:175-192, 1988.
5. Stellman, Steven D., and Stellman, Jeanne M., "Estimation of exposure to Agent Orange and other defoliants among American troops in Vietnam: A methodological approach," American Journal of Industrial Medicine 9:305-321, 1986.

and the computerized records of herbicide spraying (from the HERBS and Services HERBS tapes), taking into account time and distance from spraying. The authors make a number of claims for this methodology, the most general being that it "can be profitably used in most epidemiologic studies of the effects of herbicides on U.S. troops." Further, that "the accuracy and precision of the method are comparable to, or exceed, those used in many major environmental and occupational studies." They state that "a sizeable number of individuals were classified as 'high' exposure," and that the data "make the convincing point that sufficient numbers of troops are available and identifiable for epidemiologic study of herbicide effects."

The American Legion exposure estimation method suffers from more severe problems than did CDC's earliest attempt at an exposure index, which OTA rejected. The most serious of the problems with the exposure estimation method are:

1. Self-reported location data: Nearly 20 years after the fact, veterans were asked to recall each location at which they spent time during their tour of duty in Vietnam. Especially for men who moved around frequently (probably those in combat), this is an almost impossible feat.

2. Locations were chosen from a list of place names provided in the questionnaire. While men might have been near a particular town, large US bases, where many men were stationed, and where combat troops were likely to be, were not in the middle of towns. The place names may refer to places many miles off, yet it was presumably these actual towns that the American Legion researchers

used as points of "location," from which the distances to spray coordinates were calculated. It is impossible to judge the accuracy of this method, and the investigators provide no information to support their claim that the method is "precise and accurate." In fact, it appears to be far less precise than CDC's method using grid coordinates from military records of troop locations.

3. There is no discussion of missing data, yet there must have been significant gaps in the information reported on the questionnaires. If gaps were ignored, as seems likely, it is possible that reporting a lot of places or accounting for a greater percentage of the tour of duty would produce higher scores. This is one point on which no information is found in the papers.

4. Any location up to 15 kilometers away from a spray path coordinate virtually any time--including years later--after spraying, is considered in the exposure zone, the scores diminishing with increasing distance from the coordinate. The highest exposure score appears to be given for being within 5 kilometers of spraying. The experimental data that exist from trials at Eglin Air Force Base, which, while not necessarily definitive are the best available, suggest that virtually no Agent Orange would have travelled more than 2 kilometers from the spray line, and even at that distance, the amounts were minuscule. In CDC's analyses, nearly all troop locations that were "within 5 kilometers" of spraying were actually beyond 2 kilometers (i.e., between 2 and 5

kilometers), so even what is considered to represent the highest exposure in the American Legion study would likely have been almost no exposure at all in most instances. While it is entirely possible that some people were within 2 kilometers of spraying, particularly some time after spraying, they would likely be in the minority. The rationale for including distances up to 15 kilometers does not appear to be supportable given the set of facts available.

The investigators do not give examples of other occupational or environmental studies that have less precise and accurate exposure measures, but at least in studies of herbicide or dioxin exposure, this is not true. Several studies have focused on occupational groups with known, direct exposure, including the studies of Swedish foresters, the current NIOSH studies of chemical production workers, and the Air Force Ranch Hand study. NIOSH and the Air Force are also measuring residual dioxin in the body by means of blood serum testing. Studies of heavy environmental exposure in Missouri and Seveso include groups with known, direct exposure. In no case would a person living 15 kilometers from where herbicides were sprayed be assumed to have had significant exposure, unless some direct exposure could be documented. A person living even 5 kilometers away from a plant producing a dioxin-contaminated chemical would in no way be considered exposed comparably to workers in the plant, even if some dioxin were entering the general environment from the plant. While everyone acknowledges that conditions in Vietnam were different in many ways, there is no evidence suggesting that a scenario as unlikely as that underlying the American Legion exposure estimation method existed.

The comment that a "sizeable" number of men were classified as having had high exposure is misleading. Although no description is given of the method used to divide the group into low, medium, and high exposure categories, it appears that divisions were made to create groups of convenient size for analysis. This conclusion is based on examining the "Agent Orange Exposure Index" distribution in Figure 3 (page 120) of the first paper.[6] It is clear that most of the 557 men classified as having had "high" exposure were very nearly the same as those classified as "medium," and that the entire range of scores, except for a few men in a long tail in the high end, was quite tight. Any array of individuals with specific numeric scores, which can vary by even small amounts, is divisible arbitrarily into groups, but doing so is not necessarily meaningful. To give a simple example, a man who was 10 kilometers from a spray would presumably have a higher score (for that occasion) than a man who was 15 kilometers, but in all likelihood, neither had a significant exposure, even if one is called "high" and the other "medium."

The authors claim a measure of validity for this index because they say that men could not have known, by the information they provided, how they would be classified. But according to data presented in the 1978 paper, men's self-reports of exposure were predictive of their exposure status as calculated. This could be due to the high correlation of the Agent Orange and combat indexes, suggesting that, in general, men who scored higher on the subjective combat exposure index also believed they had been more exposed to Agent Orange (and ultimately reported more health problems). Because of the gross imprecision represented by the Agent Orange index, the idea that it was actually measuring something else is a plausible explanation for the findings.

6. Stellman, Steven D., Stellman, Jeanne M., and Sommer, John F., Jr., "Combat and herbicide exposures in Vietnam among a sample of American Legionnaires," Environmental Research 47:112-128, 1988.

CDC's final exposure assessment method, used in their "validation study,[7]" was superior to the American Legion method. When CDC arrayed their scores, the range was quite small, with very few who had objectively high scores. This lack of clearly defined high exposure was borne out by the results of serum dioxin testing. In that study, the group of men who had served in heavily sprayed areas in Vietnam had dioxin levels no different from a similar group of men who had served elsewhere. If there were, in fact, large numbers of ground troops with high exposures, it is possible that CDC's method would have identified them accurately. The finding of only "background" dioxin levels in the ground troops contrasted sharply with significantly elevated levels in a group of Ranch Hands with known, direct exposure,[8] providing assurance that a heavily exposed group is easily identifiable from one with low exposure even 15 or 20 years after the exposure ceased. The American Legion study refers to testing for residual dioxin in the body as a means of detecting past exposure as "yet to be validated." That statement appears to be inaccurate, in light of CDC's study, a similar study conducted under the auspices of the New Jersey Agent Orange Commission[9] (co-authored by Michael Gochfeld, who wrote the editorial[10] in Environmental Research that accompanied the American Legion study reports), as well as

7. CDC Veterans Health Studies, "Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in US Army Vietnam-era veterans," JAMA 260:1249-1254, 1988.
8. CDC Agent Orange Projects Office, "Comparison of serum levels of 2,3,7,8-TCDD with indirect estmates of Agent Orange exposure in Vietnam veterans," typescript, August 1987.
9. Kahn, Peter C., Gochfeld, Michael, Nygren, Martin, et al., "Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange-exposed Vietnam veterans and matched controls," JAMA 259:1661-1667, 1988.
10. Gochfeld, Michael, "New light on the health of Vietnam veterans," (editorial), Environmental Research 47:109-111, 1988.

studies of heavily exposed Missouri residents[11], and recent results of serum dioxin testing in individuals living in a dioxin-contaminated area near Seveso, Italy[12].

The editorial accompanying the American Legion Studies[13] erroneously states that the Government's decision to halt the Congressionally mandated Agent Orange study was a result of CDC "arguing nihilistically that since exposure cannot be well documented, the study was not feasible." This is not true. The decision was made because of compelling evidence, from serum dioxin testing and the military records, that there did not exist a large group of ground troops with significant exposure. The American Legion study has done nothing to alter this set of facts.

Study Population

The participants in the American Legion study are referred to as a "random sample" of male Vietnam-era Legionnaires from six States. However, this does not appear to be the case, and the divergence from the ideal of a random sample could well have been responsible for some of the reported differences in health and other outcomes reported. The procedure for identifying potential participants describes an initial list of randomly selected names of American Legionnaires in the six States included in the study. Later in the process, 770 "volunteer researchers" were used to contact people on the lists to determine their time and place of service. Each

11. Patterson, D.G., Jr., Needham, L.L., Pirkle, J.L., et al., "Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri," Arch. Environ. Contam. Toxicol. 17:139-143, 1988.
12. Mocarelli, P., Pocchiari, F, and Nelson, N, "Preliminary report: 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure to humans--Seveso, Italy," MMWR 37(48):733-736, 1988.
13. Gochfeld, Michael, "New light on the health of Vietnam veterans," (editorial), Environmental Research 47:109-111, 1988.

volunteer was given a list of about 200 names, with the charge of identifying 15 SEA and 15 non-SEA Vietnam-era veterans. There is no suggestion that these volunteers contacted people on the list in a random order. Though the procedure is confusingly presented, it appears that once 15 from each group were identified, the volunteer could stop. This introduces some selectivity by the volunteers, the effect of which is unquantifiable. In a study of this type, it is important that the participants be selected independent of any characteristics other than their having served in Southeast Asia (for the SEA group) or having served elsewhere in the military during the Vietnam era (for the non-SEA group).

A second potential problem is participation bias. Once having received a questionnaire from the investigators, those who had been identified by the volunteers decided whether or not to participate. Every study that depends upon individuals freely choosing whether or not to participate has a potential problem with response bias. The greater the influence of other factors on selection into the study, particularly, for instance, if SEA veterans were more likely to participate if they had many health problems than if they were relatively healthy, the greater the potential for ending up with spurious results. The effects of this type of bias can be minimized in a number of ways. First, investigators attempt to get a high response rate from both groups, so that the "non-responders," even if they had participated, would have had little effect on the results. The overall response rate in the American Legion study was poor, reported to be between 52.5% and 64.1%, although it is impossible to determine, based on the information given, the precise response rate. The authors claim that the sample is not significantly biased, but in the many figures they cite, and in the discussion, they do not include a simple comparison of the response rates of SEA veterans and non-SEA

veterans separately, which is of fundamental importance. The information presented to substantiate their claim that the sample is not unduly biased and is representative of the class of veterans they represent is inadequate.

The low overall response rate and the potential bias introduced by the volunteer researchers suggest that the study population may not fairly represent the groups to which they belong, and that differential influences on response between SEA and non-SEA veterans, and possibly among various subgroups of SEA veterans may have affected the results significantly.

Problems with Self-Reported, Unverified Information

This study depends entirely on information about "exposures" and a whole range of health and other outcomes. Nothing was verified by objective data. CDC's Vietnam Experience Study[14] (VES) clearly demonstrates that self-reporting of health events and reproductive history can lead to the erroneous conclusion that Vietnam veterans, and those who believe they were exposed to herbicides, have more health problems than non-Vietnam veterans and Vietnam veterans who do not believe they were exposed, respectively. Except for a small number of specific conditions (e.g., hearing loss), these differences were not borne out in the VES by standardized, detailed physical examinations, nor was a reported excess of birth defects among the children of Vietnam veterans confirmed when all birth records were examined. These differences can occur because of underreporting by one group, overreporting by the other, or a combination of the two. It is not necessarily a result of individuals knowingly misreporting, but can be explained by differential recall.

14. CDC Vietnam Experience Study, "Health status of Vietnam veterans," JAMA 259:2701-2719, 1988.

Taking a specific example, the SEA veterans in the American Legion study reported significantly more skin problems than did the non-SEA veterans. Those who reported actually handling herbicides (and therefore would clearly have known that he would be in an "exposed" category) reported higher rates than SEA veterans who did not report handling herbicides. In addition, there was an increasing tendency to report skin conditions with increasing Agent Orange scores (though that association could be related to combat scores rather than Agent Orange scores) among the SEA veterans. In the VES, a similar excess of self-reported skin conditions was found. However, on physical examination, including an examination for scars of past skin problems, there was no difference between the two groups in the prevalence of any skin condition. With no corroboration of these differences based only on self-reporting, the American Legion study findings cannot be taken as evidence for real differences in health history or current health status.

The American Legion investigators claim that participants' health reporting could not have been influenced by prior knowledge of their Agent Orange exposure scores, therefore associations with Agent Orange are not the result of biases in response. This contention is not supported by the data presented, however. First, as discussed earlier, self-described exposure was correlated with exposure scores in the 1986 study. Second, Agent Orange exposure scores were highly correlated with combat scores. Combat scores were based on eight questions about experience in SEA, which in all likelihood led to a ranking reflecting mainly men's perceptions of how extreme their combat experiences were. The questions were all answered subjectively, the participant choosing between "never," "rarely," "sometimes," "often," and "very often," to describe the frequency of eight types of experiences, e.g., firing his weapon at the enemy, killing the enemy, seeing someone killed, etc.

The way a veteran feels about and has dealt with his war experience in general is bound to affect the way in which he answers these questions. While this scale may be a valid measure of how a veteran perceives his wartime experience, which is of clear importance, it has not been validated against military records to determine whether these answers correspond to the veteran's actual experience. Nonetheless, the American Legion study uses this combat index as though it were an objective measure.

Issues Related to PTSD Assessment

The definition of PTSD in this study is based on use of the combat scale (eight questions) as a surrogate for identifying a traumatic event, and questions about PTSD symptoms, as defined by the Diagnostic and Statistical Manual of Mental Disorders ("DSM-III"). By arbitrarily defining different cutoffs and combinations of combat scores, the investigators arrive at different rates of PTSD among the SEA veterans. They refer to numbers of men "diagnosed" or with a "clinical diagnosis," though, in fact, none of the specific measures they use have been validated against the standard, which is a diagnosis based on an in-person clinical examination. The fact is that some particular percentage of these men actually has PTSD, and more have some symptoms of it. The actual numbers may be in the range circumscribed by the above estimates, but it is not possible to base conclusions about specific rates on this study.

Although validation of the questions used to define PTSD is mentioned, the claims are unsupported and in some cases misleading. The authors claim that the combat scale has been validated, but whether it has or not, it was not designed as a surrogate for detecting a traumatic event, but as a measure of combat. Any validation refers only to that. There is no evidence that the

particular questions about PTSD symptoms used in this questionnaire, specifically self-administered, are a valid means of collecting this information.

At this point, with the National Vietnam Veterans Readjustment Study (NVVRS) and the VES completed, it is clear that PTSD is a real and significant problem for Vietnam veterans. Those two studies were better designed than the American Legion study, particularly the NVVRS, which did use a clinical examination to validate the in-person questionnaires on which PTSD prevalence estimates were based.

The Questionnaire

Two kinds of problems with the questionnaire itself, in addition to those already mentioned, may have affected the validity of various outcomes reported by the investigators. These problems include the "demand characteristics" of the questionnaire and several instances of faulty logic.

Demand Characteristics

It is well known that the way in which questions are asked can influence the answers given, and these influences are known as demand characteristics. In the American Legion study questionnaire, the questions that might evoke negative feeling--e.g., about combat situations, about exposures to chemicals in the military, about flashbacks and anxieties--are asked first. Then the questions about happiness, satisfaction, and health are asked. This tends to set up certain hypotheses in the minds of participants as the questionnaire progresses.

The wording of some individual questions also suggest hypotheses. For example, one set of questions (which are obviously related to PTSD) is introduced with the statement: "Serving in the military often puts us in

situations that stay in our memories for a long time." The first question then asks: "...how often have you: Had vivid recollections of your military services, especially bad scenes?" The introduction to the question sets up a situation in which the respondent would be encouraged to report recollections. If a person reported that he never or rarely has recollections, his response would be contrary to the statement made in the questionnaire. Answers to the rest of the questions in that group could be affected similarly.

Another example is a multipart question that begins with: "When all things are considered, to what degree were your military experiences stressful?" The next part of the question asks: "Taking all things together, how happy are you these days?" and then "In general, how satisfying is your life?" The grouping of these questions forces the respondent to evaluate happiness and satisfaction today in light of the level of stress he experienced in the military, as though there necessarily is a connection.

Faulty Logic

The American Legion questionnaire, like many questionnaires, contains groups of questions that do not apply to all participants. To deal with this, "skip patterns" are built into it. For instance, the non-SEA veterans are told appropriately to skip the section on SEA military service. In two major instances, however, in the sections on drinking alcohol and the one dealing with family/marital relationships, inappropriate skips are introduced. The data on both subjects are reported in the papers with no mention of this problem, nor with any suggestion that the responses apply only to a portion of the respondents.

In the section entitled "Beverages, Tobacco and Medication," question 5 asks: "Do you drink alcoholic beverages?" If the answer is "No," the instruction is to go on to question 13. If yes, one continues with 6 through 12. Questions 6, 7, and 8 concern current drinking habits, and are skipped appropriately. Questions 9 through 12, however, should apply equally to former drinkers, e.g., question 10, which reads: "Has there been a change in your drinking habits since your discharge from the service?" The choices are: "no change," "yes, I drink more," or "yes, I drink less." Question 11: "Have you ever had a serious drinking problem?" Question 12: "Have you ever found yourself unable to consume alcohol even when you felt like it?" No other questions that would elicit the information that a respondent had stopped drinking are asked.

In the introduction to the section on family and marital relationships, respondents who had "lived alone for the past six months" are instructed to skip the entire series of questions. However, within the section to be skipped are questions directed clearly at men living alone: "If you have not lived with another person during the past six months have you had any friends of the opposite sex that you have enjoyed being with?" In addition, a battery of questions concerning relationships with children are skipped. No rationale for this is given in the paper reporting these results, and they are reported as though they apply to the entire study sample.

In both of these cases (drinking alcohol and relationships), the information collected is incomplete, and the questionnaire may have been confusing to the respondent, making the accuracy of the reported results highly suspect.

Office of General Counsel Washington, D.C. 20420

Veterans Administration

January 30, 1989 In Reply Refer To:

Honorable G.V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is to advise you that the series of papers reporting on the health status of Vietnam era veterans w o are members of the American Legion which were recently published in Environmental Research (vol. 47, pp. 129-209, (1988)) will be reviewed at the next meeting of the Veterans' Advisory Committee on Environmental Hazards (currently scheduled for April 25 and 26, 1989). Due to conf icting schedules of Committee members, it is not feasible to convene a meeting of the Committee or of the Dioxin Panel prior to that date for the purpose of discussing these papers. However, Dr. Yanders, the Chairman of the Committee's Scientific Council has reviewed the papers and has prepared a summary of his personal views on them. I am enclosing that summary for your information.

A similar letter is being sent to the Chairman and Ranking Minority Members of the House and Senate Veterans' Affairs Committees. If I can be of further assistance, please let me know.

Sincerely,

Frederic L Conway for

OLIVER H. MEADOWS
Chairman, Veterans' Advisory
Committee on Environmental Hazards

Enclosure

"America is #1—Thanks to our Veterans"

21-414 O - 89 -- 6

Evaluation of the Studies by the Stellmans and Their Associates, Environmental Research 47 (1988).

1. The major problem with this work is apparent in the first paper, which asserts that "categorization of Vietnam Veterans according to herbicide exposure can be successfully accomplished, based on an existing detailed herbicide application data base." No data are cited. There is no support for this position. In fact, the far larger, far better designed study earlier begun by CDC was abandoned precisely because no such exposure could be established from the records of pesticide application and troop movements.

2. The second problem, of almost equal magnitude, is the total reliance of the investigators on a self-administered questionnaire with no attempt at confirmation. Such procedures are notoriously prone to errors for which "internal checks" alone are not sufficient.

3. In a contentious and self-serving editorial in the same issue of the journal which contains all five papers, Gochfeld refers to them as "a remarkable series of epidemiologic studies." They are indeed remarkable for their far-reaching conclusions based on inadequate and faulty evidence. The editorial also is heavily biased against the CDC and VA, and plays upon the emotions of the reader by implying that the failure of more rigorous studies to find increased levels of morbidity and mortality in the population studied is evidence that the Vietnam Veterans continue to be mistreated because of their participation in an unpopular war. The editorial - and the papers themselves - adopt an "us against them" tone, in which "us" are those who agree with this position, and "them" are everyone else. The papers selectively cite work which supports their position and largely ignore that which does not.

4. The inclusion of Post-Traumatic Stress Disorder (PTSD) in the study confuses the issue. By this inclusion, Agent Orange is implicated by association, but the authors do not even suggest a relationship. It is also interesting to note that no data on PTSD are given for those veterans who did not fall into the "median or above" combat category.

5. The studies involve a population that is considerably different from the Vietnam Veteran as a whole, in that it is (a) predominantly white, (b) predominantly Northern, and (c) predominantly Midwest. There is also the likelihood that being a Legionnaire is more prevalent in certain social classes than in others. Even if its conclusions were correct, this work is on shaky grounds when it attempts to speak for "the Vietnam Veterans."

6. These studies contain nothing of value to the V.A., and should be completely disregarded.

January, 1989 — Armon F. Sanders

Office of General Counsel Washington, D.C. 20420

Veterans Administration

JUN 2 1989

JUN 2 1989

In Reply Refer To:

Honorable G. V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Shortly after the publication of a series of papers reporting on the health status of Vietnam era veterans who are members of the American Legion were published last September you wrote to me requesting the views of the Veterans' Advisory Committee on Environmental Hazards concerning these papers. The papers were reviewed by the Committee at its April meeting and I am enclosing a copy of the Committee's assessment.

A similar letter is being sent to the Chairman and Ranking Minority members of the House and Senate Veterans' Affairs Committees. If I can be of further assistance, please let me know.

Sincerely yours,

Frederick L'Conway

for Oliver Meadows
Chairman, Veterans' Advisory Committee
on Environmental Hazards

Enclosure

The Veterans Advisory Committee on Environmental Hazards at its April 1989 meeting reviewed a series of papers reporting the results of a study of randomly selected members of the American Legion who had military service during the Vietnam era. The authors sought to analyze information on the personal, reproductive, family, and mental health of the veterans, and on health behaviors, such as smoking, drinking, and drug use, and to determine the extent to which these factors varied with respect to exposure to combat and herbicides. In the first paper,"Combat and Herbicide Exposures in Vietnam among a Sample of American Legionnaires" (Stellman, et al., Environ. Res. 47: 112-128 (1988)), the authors analyzed the patterns of exposure to combat and herbicides.

The study population was derived from American Legion members in six states (Colorado, Ohio, Maryland, Pennsylvania, Indiana, and Minnesota). The randomly selected participants were mailed a self-administered questionnaire.

The authors noted that "(e)stimation of exposure to herbicides such as Agent Orange in Southeast Asia is without doubt the most difficult component of the entire study." They used a probabilistic exposure index based upon the Department of Defense's HERBS tape and supplementary files developed by the U.S. Army and Joint Services Environmental Support Group in conjunction with the subject's self-reported recall as to his geographic location in Vietnam. The authors noted the data used in the construction of the index were "derived from respondents' self-reports of locations in Vietnam, and, as such, are subject to recall error. Nevertheless," the authors stated, "subjects appear to have exercised considerable care filling out this portion of the survey." The index of exposure was described as counting all sprayings which ever occurred near each location reported by the veteran and was weighted inversely according to distance and exponentially according to elapsed time. The authors did not provide evidence that the exposure index is a valid measure of actual exposure to herbicides, and blood or tissue levels of dioxin or other chemicals were not measured.

To measure combat exposure, the investigators asked eight questions which sought to characterize the extent to which the respondents had undergone traumatic combat experiences. Again, the authors did not provide evidence that their calculated combat index is, in fact, a valid measure of actual combat exposure.

The authors concluded that this (or similar) methodology could be used in most epidemiologic studies of the effects of herbi-cides on U.S. troops. The Committee had serious reservations about the scientific validity of this paper. Particular criticism was directed towards the authors' indices of exposure for both Agent Orange and combat. With respect to Agent Orange, the Committee noted the complete reliance upon the HERBS tapes and the recall of the study's participants. The authors provided no evidence

to support the validity of the exposure indices. The failure to do so, in the opinion of the Committee, constitutes a serious flaw in the study design, and raises serious questions about the validity of the authors' conclusions. The authors themselves commented that they realized that the "classification of exposure to herbicides of Vietnam veterans is fraught with controversy" and commented that they had addressed the methodological issues previously.

The Committee believed that the authors relied excessively upon the presumed accuracy of the HERBS tapes as indicators of spray paths. The members observed that the tapes can be very inaccurate and not representative of actual combat missions in Vietnam. Also, assumptions concerning the dispersal of the herbicide, particularly the authors' failure to consider the biological degradation and absorption by the foliage, were a source of concern to the Committee.

Another limitation of the study involves the possible bias due to non-response. The authors indicated that "return rates ranged from a low of 52.5% in Pennsylvania to a high of 64.1% in Minnesota." The Committee commented that a health survey with such low response rates is at best questionable with respect to its validity. A survey with a response rate below 75%, the Committee observed, is relatively prone to bias. The authors attempted to address this issue when they stated that "the critical question is whether the distribution on important variables differs between men coming from high response Posts, compared with men from low response Posts." The authors then went on to state, "(they) examined the relevant distributions of many variables and found no differences that could have affected the study results materially." The Committee observed that such comparisons do not involve veterans who did not respond, and, therefore, fail to address the issue of non-response bias. In the opinion of the Committee, the authors' argument appeared contrived leaving the possibility of nonresponse bias a serious limitation of the study. Additionally, the authors failed to provide information about possible differential response rates between the Southeast Asia group and the control group. A differential response rate could be another source of bias.

The Committee also expressed reservations about the reliance upon self-reporting. The Committee observed that both the Centers for Disease Control's Vietnam Experience Study and the Ranch Hand study demonstrated the occurrence of bias when self-reporting was used to assess health effects. Stellman, et al., made no effort to verify the responses by physical examination or medical record review.

Self-reporting bias may also affect the calculated exposure indices. There was apparently no attempt to validate the veterans' responses by comparing them to the pertinent military data.

The Committee concluded that because of its serious flaws in design, the study could not provide valid information about exposure to herbicides or to combat.

The Committee then reviewed the paper entitled, "Social and Behavioral Consequences of the Vietnam Experience among American Legionnaires." (Environ. Res. 47: 129-149 (1988).) The authors reported their analyses of the data acquired as described in the preceding paper. Combat and exposure to herbicides were considered as independent variables. The analyses involved multiple regression that included terms for combat and Agent Orange exposures as well as a term for their interaction.

The authors reported a wide range of adverse effects. Vietnam combat veterans were found to have significantly lower family income irrespective of their educational levels. Men who experienced high levels of combat intensity were found to be at greater risk for divorce or separation. With regard to sexual satisfaction, the authors found statistically significant terms in the multiple regression model for combat exposure and for its interaction with Agent Orange. The Agent Orange term itself was not significant. The authors stated, "This result, where herbicide is not an independent predictor but only enters the equation in an interactive term, suggests that herbicide effect which is manifest only at very high levels of combat is present." The authors found, however, that in similar analyses of parental and marital outcome only combat was significant; neither Agent Orange nor the interaction term were significant.

With regard to psychological well-being, the authors employed five measures: depression, anxiety, helplessness/hopelessness, degree of anger/irritation, as well as physical symptoms of depression. All five scales were significantly associated with combat. For Agent Orange exposure, however, none of the five scales, after adjustment for combat exposure, showed an association. Consumption of alcoholic beverages was the only other variable analyzed with respect to Agent Orange exposure. After controlling for the effects of combat, the results revealed no association.

The authors concluded, "(O)ur data give some indication that certain behavioral effects related to combat intensity may be exacerbated by concurrent exposure to herbicides and indicate the need for further exploration of this issue....Further study, with a larger population, is necessary in order to control the confounding effects of combat more effectively and thereby estimate more accurately the effects of herbicides on psychological well-being."

The Committee commented that this study must be interpreted cautiously due to the serious flaws in its design and execution difficulties revealed in the previous paper. The Committee again identified major areas of concern: failure to validate the measure of Agent Orange exposure, potential bias due to the low study response rates, and the total reliance on self-reporting without independent verification of the data. It was also observed that the observed effects were often relatively small. The effects may be statistically significant but biologically unimportant.

The Committee then reviewed the paper, "Health and Reproductive Outcomes among American Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam." (Stellman, et al., Environ. Res. 47: 150-174 (1988).) The authors noted that the study was not designed to investigate the possible relationship between herbicide exposure and the development of malignancies. The authors stated, "Because of the low background rates of all types of cancer in a group with this age distribution, the present study does not have the statistical power to detect such effects. Also for the majority of the cohort, insufficient time has elapsed for the natural latency of the disease process to have passed."

For health conditions, the investigators found statistically significant increased associations for herbicide handlers versus non-handlers in regard to reported histories of hypertension, heart disease, ulcers, sensitivity to light, change in skin color and skin rash with blisters. With regard to dose response relationship, the authors found statistically significant associations of herbicide exposure with histories of benign fatty tumors, adult acne, increased sensitivity to light, and skin rash with blisters.

By means of factor analysis, the investigators determined five symptom scales: faintness, fatigue or physical depression, aches and pains, colds, and skin effects. For each of these scales, the mean among herbicide handlers was significantly higher than among nonhandlers. Multiple regression with terms for combat exposure, Agent Orange exposure and their interaction revealed statistically significant associations for each of combat and Agent Orange exposure with all five symptom scales. In these analyses, generally, combat exposure had the stronger relation compared with Agent Orange exposure.

For reproductive effects, the authors confined their analysis to ever-married men born in 1940 or later. With regard to dose-response relations with Agent Orange exposure, after adjustment for level of combat, no significant association was found for: difficulty having children, delay in fathering (defined as the time elapsed between the end of military service and the first reported pregnancy of a spouse), number of pregnancies fathered, gender of liveborn children, and birth weight of live-born

children. The one reproductive outcome where the investigators did find a significant association with Agent Orange exposure was miscarriages.

The authors commented that "while the manifold effects noted in this study span a wide range of outcomes, they are by no means haphazard, but in fact constitute a set of highly specific endpoints, most of which were initially chosen for study because of previous reports in the literature on exposure to stress and to phenoxy herbicides or TCDD....These findings on physical and reproductive health are consistent with and mutually reinforce the conclusions of the other papers in this series concerning the pervasive effect of combat and herbicide exposure on the lives of veterans of the Vietnam war."

The Committee commented that this paper is subject to the same serious criticisms as the other studies in this series because of flaws in design and execution. Also, this particular study has the additional statistical limitations associated with making multiple comparisons.

Finally, the Committee reviewed the paper entitled, "Post-traumatic Stress Disorder among American Legionnaires in Relation to Combat Experience in Vietnam: Associated and Contributing Factors," by Snow, et al. (Environ. Res. 47: 175-192 (1988).) The authors stated four goals. Those were to examine (1) the frequency of combat-related PTSD and its components in a large, randomly selected sample of Vietnam veterans, (2) the nature of the precipitating factors that are necessary for PTSD to be experienced, (3) the etiologic roles of selected demographic and precombat health variables upon the development of PTSD, and (4) the stability of the PTSD symptom complex over time. The authors reported their various findings and concluded that their research provided strong evidence for the existence of PTSD in a large nonclinical sample of Vietnam veterans and that the symptoms were most likely to occur in individuals who had higher levels of traumatic combat exposure.

The Committee did not consider this paper to be relevant to its charge as it did not involve Agent Orange or herbicide exposure. The Committee noted that the study contained the same design flaws as the other papers and that, consequently, the authors' conclusions are open to serious question.

ALAN CRANSTON, CALIFORNIA, CHAIRMAN
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ANTHONY J. PRINCIPI, MINORITY CHIEF COUNSEL/STAFF DIRECTOR

United States Senate

COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

September 22, 1988

Mr. Oliver H. Meadows
Chairman
Veterans' Advisory Committee
on Environmental Hazards
Veterans' Administration
Washington, D.C. 20420

Dear Oliver,

As you may know, the enclosed report, entitled "CDC Blood-Dioxin Validation Study" was published in the September 2, 1988, edition of The Journal of American Medicine.

The final results of this blood validation study showed no association between serum dioxin levels and the Agent Orange exposure experience among the Vietnam veterans studied as evidenced by their military records, regardless of whether those records or self-reported estimates indicated high, low, or intermediate exposure. Moreover, all except two of the Vietnam veterans tested showed dioxin levels within normal background levels -- that is, the upper limit for United States residents without known dioxin exposure.

As the Chairmen and Ranking Minority Members of the Senate and House Committees on Veterans' Affairs, we are requesting that the Veterans' Advisory Committee on Environmental Hazards review and provide comments on this report. In particular, we would appreciate your evaluation of the scientific methods used and of the validity of the statistical analysis. We would also appreciate your identification of any specific findings discussed in the report which warrant follow-up investigation or analysis.

With warm regards,

Cordially,

Alan Cranston
Chairman

G.V. (Sonny) Montgomery
Chairman

Frank H. Murkowski
Ranking Minority Member
Senate Committee on
Veterans' Affairs

Gerald B.H. Solomon
Ranking Minority Member
House Committee on
Veterans' Affairs

Enclosure

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JAN 19 1989

The Honorable G.V. (Sonny) Montgomery
Chairman
House Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515-6375

Dear Mr. Chairman:

As promised in my recent letter, the Science Panel of the Domestic Policy Council Agent Orange Working Group (DPC/AOWG) has reviewed the American Legion Epidemiologic Studies of Vietnam Veterans (Environmental Research 1988; 47109-209). At a specially convened meeting of the DPC/AOWG on January 10, 1989, their evaluation was reviewed and received concurrence.

In sending you the review, I include the letter and summary of findings from the Chair of the Science Panel. Of particular note, we have included the individual opinions of each scientist by name. Missing from the individual opinions is that of the representative from the Congressional Office of Technology Assessment (OTA) who contributed much to our deliberations. OTA will be making its own review and report under separate cover.

In sending this report, I also bid farewell as the Chairman of the DPC/AOWG. The important work of research will continue under new leadership until this vital issue is resolved.

It has been a privilege to have served our Nation's veterans and to have worked with you in the process.

With warm personal regards,

Sincerely,

Don Newman

Don M. Newman
Chairman
Domestic Policy Council
Agent Orange Working Group

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333
(404) 488-4111
or FTS 236-4111

JAN 0 5 1989

MEMORANDUM TO: Members, Science Panel, ACWG

FROM: Chairman, Science Panel, ACWG

SUBJECT: Review of the American Legion/Stellman Papers

Attached are copies of the reviews we have received to date on the subject study. There will be a Science Panel meeting from 11 a.m. to 1 p.m. January 10, 1989, in the Under Secretary's Conference Room, 6th Floor, Hubert Humphrey Building, to discuss this and attempt to prepare a final document for transmission to ACWG. This will be followed at 2 p.m. by a joint meeting of the ACWG and the Science Panel in the same room.

I am personally not involved in this review process but am only the convener of meetings and the sender of papers. Dr. Stephen Thacker, Assistant Director for Science, Center for Environmental Health and Injury Control, is taking the lead in coordinating these responses and preparing the final document.

Sincerely yours,

Vernon N. Houk, M.D.
Assistant Surgeon General
Director
Center for Environmental Health
and Injury Control

Attachments

cc:
Dr. Stephen Thacker

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

(404) 488-4111
or FTS 236-4111

January 9, 1989

MEMORANDUM TO: Mr. Don M. Newman
Chair, Domestic Policy Council, Agent Orange Working Group

FROM: Chair, Science Panel, Agent Orange Working Group

SUBJECT: Review of the American Legion Study Papers Published in Environmental Research, December 19, 1988

Because of concern about my own potential bias, I did not direct or participate in this review The response from the Center for Environmental Health and Injury Control, Centers for Disease Control, were coordinated by Stephen B. Thacker, M.D., M.Sc., Assistant Director for Science, who also chaired the meeting of the Science Panel. My role was limited to convener and movement of paper to the various members of the Science Panel.

The Science Panel did not review the final article in the series entitled "Utilization, Attitudes and Experiences of the Vietnam-Era Veterans with the Veterans Administration Health Facilities: The American Legion Experience,in great detail. However, the Science Panel concurs with the reviews done by Dr. Han K. Kang and Dr. Lawrence B. Hobson of the Veterans Administration, which are attached as a portion of this communication.

Despite several requests, we were never able to obtain the protocol for this study. We did obtain a copy of the questionnaire but from a source other than the American Legion or the authors of the papers.

Included for transmission to the Congress is a summary review of the nine responders from the Center for Environmental Health and Injury Control, CDC, in addition to their individual reviews. Also included are reviews from Dr. Lawrence B. Hobson and Dr. Han K. Kang of the Veterans Administration; Dr. Manning Feinleib, Director, National Center for Health Statistics, CDC; Dr. Marie Sweeney from the National Institute of Occupational Safety and Health, CDC; Dr. Jeff Lybarger of the Agency for Toxic Substances and Disease Registry, Public Health Service; Colonel William H. Wolfe of the Department of the Air Force; Dr. John F. Young of the Natoinal Center for Toxicological Research, Food and Drug Administration; Dr. Donald Barnes of the Environmental

Protection Agency; and Captain David Uddin of the Department of Defense, accompanied by a review prepared by Dr. Jerome Bricker, consultant to the Department of Defense, regarding the article, "Combat and Herbicide Exposure in Vietnam Among a Sample of American Legionnaires" by Stellman, et al, American Journal of Industrial Medicine 9:305-321 (1986), which apparently was the basis for the herbicide exposure cited in the American Legion studies.

The following is the review by the Science Panel.

The data presented in the American Legion report of the Epidemiologic Studies of Vietnam Veterans (Environmental Research 1988; 47:109-209) do not support the conclusions drawn by the authors. The study is seriously flawed due to major problems in study design and execution. First, there is potential selection bias due to non-random sampling and low response rates. Second, there is potential information bias due to poor questionnaire design and the analysis only of self-reported data without external validation. Probably of greatest concern, any observed association between combat or herbicide exposure is confounded by the investigators' use of subjective measures of combat and herbicide exposure. Combat exposure was not validated by comparison with military records. The herbicide exposure index used by the authors has not been validated, and based on the Agent Orange Validation Study and the Ranch Hand Study, does not accurately predict exposure. Because of these problems, the results of the American Legion report are of little or no value in further understanding the Agent Orange issue. The collective decision of the Government not to proceed with the CDC Agent Orange Study was correct and is not affected by the American Legion report.

Interpretion of the findings are made more difficult by the absence of standard tables on demographic distributions for the original sample, the participant sample, or the sample of veterans that provided sufficient information for estimation of herbicide exposure. Some of the information provided on service experience could have been cross-checked by reviewing discharge records for at least some veterans. The American Legion reports as well as the accompanying editorial imply erroneously that evaluating herbicide exposure in this study is not much different than in retrospective studies of exposure to workers where individual exposures are not measured. The analogy is misleading because in well-conducted occupational studies, one knows from objective records that the employee was in an area of potential exposure and that workers are exposed during operations. In contrast, in the American Legion study, we do not know if veterans were within miles of a sprayed area, and we do not know if any dose, let alone a measurable dose, was received.

Discussion of the findings of the American Legion study is incomplete. Findings from the Vietnam Experience Study (VES), the Agent Orange Validation Study, and other important studies should have been addressed more thoroughly. For self-reported health outcomes, the results are similar to those obtained with the VES questionnaire. As with the American Legion study, almost all outcomes in the VES were reported more often by Vietnam veterans than by other Vietnam-era veterans. Those Vietnam veterans who reported either handling herbicides or having more combat experience also reported higher rates of most outcomes. Most of the verifiable self-reported

conditions, however, were not substantiated by objective evidence obtained during the physical examination. It is not clear why the authors of the American Legion papers, as well as the author of the accompanying editorial, ignore these available data which would have helped them interpret their subjective data.

When one views the full range of the studies on Vietnam veterans, including those with detailed objective data, clear and consistent conclusions emerge:

1) Many Vietnam veterans report psychologic and physical symptoms. Psychological abnormalities have been demonstrated by objective evidence to be slightly more prevalent in Vietnam Veterans. Combat-related Post Traumatic Stress Disorder has been shown to be a problem in several studies. Almost all physical abnormalities have not been confirmed.

2) Many Vietnam veterans also were in and around herbicide or pesticide applications in Vietnam, and they have subsequently been told about dioxin and its "extreme" toxicity.

3) Many Vietnam veterans, therefore, attribute their current symptoms to past herbicide exposure.

4) Very few Vietnam veterans, unless occupationally exposed (e.g., sprayer or mixer), have been shown to absorb significant quantities of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (and therefore other harmful herbicide constituents).

Because of the selected and limited exposure of soldiers in Vietnam, studies of adverse effects produced by herbicide exposure cannot be efficiently done from general samples of Vietnam veterans. Studies which can provide more precise measures of the effect on humans of TCDD are in progress in the small number of people with serum levels of TCDD's markedly above background due to heavy and repetitive (usually occupational) exposure. The major studies are the Air Force Ranch Hand Study, the NIOSH Mortality and Morbidity studies, and the studies around the Seveso incident in Italy. Because of the documented absence of exposure in ground troops in Vietnam, even if these ongoing studies find exposure-related health effects, they cannot be applied directly to the vast majority of Vietnam veterans.

Vernon N. Houk, M.D.
Assistant Surgeon General
Director
Center for Environmental Health
and Injury Control

Review of the American Legion Study of the Health of Vietnam Veterans

Environmental Research 1988;47:109-209.

Prepared by:

Stephen B. Thacker, M.D., M.Sc.
Assistant Director for Science
Center for Environmental Health and Injury Control
Centers for Disease Control

January 4, 1989

SUMMARY

The data presented in the American Legion Study of the Health Effects of Vietnam Veterans (Environmental Research 1988;47:109-209) do not support the conclusions drawn by the authors. The study is seriously flawed due to major problems in study design and execution. First, there is potential selection bias due to non-random sampling and low response rates. There is potential information bias due to questionnaire design and self-reporting data without external validation. Finally, probably of greatest concern, any observed association between combat or herbicide exposure is confounded by subjective measures of combat and herbicide exposure without biological validation of herbicide exposure. The herbicide exposure index used by the authors has not been validated, and based upon the Agent Orange Validation Study and the Ranch Hand Study, that index is very likely to be flawed. Together, these problems make interpretation of the results of the study difficult.

The findings are made more difficult by the absence of standard tables on demographic distributions for the original sample, the participant sample, or the sample that provided sufficient information for estimation of herbicide exposure. Some of the provided information on service experience could have been cross-checked by reviewing discharge records for at least some veterans. The accompanying editorial implies erroneously that evaluating herbicide exposure in this study is not much different than retrospective studies of exposure to workers where individual exposures are not measured. The analogy is misleading because one knows from objective records in occupational studies that the employee was in an area of potential exposure, and that workers are exposed during operations. In the American Legion study, we do not know if veterans were in spray areas at the time of spraying, and we do not know if any dose, let alone a measurable dose, was received.

Discussion of the findings of the American Legion study is incomplete. Findings from the Vietnam Experience Study (VES), the Agent Orange Validation Study, and other important studies should have been addressed more thoroughly. For health outcomes, the results are very similar to the questionnaire component of VES. As with the American Legion study, almost all outcomes in the VES are reported more often by Vietnam veterans than by other veterans. Among Vietnam veterans, those who report either handling herbicides or having more combat experience report higher rates of most outcomes. Most of these associations, however, were not substantiated by the physical examination, and it is likely that in most cases the higher rates were due to recall bias. This is also probably true in the American Legion study. It is not clear why the authors of the American Legion papers, as well as the author of the accompanying editorial ignore available data that would have helped them interpret their subjective data.

When one views all of these studies, including those with very costly objective data, there is a clear and consistent alternative set of interpretations which is not at variance with any of the data reported to date by any study group:

1) Many combat veterans have psychologic and physical symptoms.

2) Many of them also were in and around herbicide applications in Vietnam, and they have subsequently been told about dioxin and its "extreme" toxicity.

3) Many of them, therefore, attribute their current symptoms to past herbicide exposure. When complaints related to physical findings were objectively evaluated in the VES, most differences between the Vietnam group and the non-Vietnam Vietnam era veteran could not be substantiated. Psychological abnormalities were found to be slightly more prevalent in Vietnam Veterans. Combat-related Post Traumatic Stress Disorder has been shown to be a serious problem in several studies.

4) Very few Vietnam veterans, unless occupationally exposed (e.g., sprayer or mixer), have been shown to absorb significant quantities of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (and therefore other harmful herbicide constituents) from the types of casual or non-repetitive exposures they experienced.

Because of the selected and limited exposure of soldiers in Vietnam, studies of adverse effects produced by herbicide exposure cannot be eff[illegible]ently done from general samples of Vietnam veterans. Studies which can pr[illegible]de more precise measures of the effect on humans of TCDD are in progress in the small number of people with heavy, and repetitive (usually occupational) exposure. The major studies are the Air Force Ranch Hand Study, the NIOSH Mortality and Morbidity studies, and the studies around the Seveso incident in Italy. Preliminary reports for two of these studies suggest the hypothesis that TCDD is substantially less toxic to man than to guinea pigs. The NIOSH studies are not yet reported.

BACKGROUND

In the December 1988 issue of Environmental Research a series of five papers appears reporting on a study of the health of Vietnam era veterans who are members of the American Legion. Funded by the American Legion and conducted by investigators at Columbia University, the first four papers describe the results of a cross-sectional study of Legionnaires from six states relating health problems to the Vietnam exposure, in particular exposure to combat and herbicides.[1,2,3,4] The fifth paper reports on Legionnaires' utilization of Veterans Administration health facilities.[5]

The results of the American Legion study are in many ways consistent with those reported by the Centers for Disease Control (CDC) as they relate to veterans perception of illness and its relationship to the Vietnam experience.[6,7,8] There are, however, striking differences when the American Legion researchers attempt to relate herbicide exposure to specific adverse health effects. Any epidemiologic study can be criticized, and what must be decided is whether sufficient care has been taken in the design, implementation, analysis, and the interpretation of the results of the study, and whether or not the methods of a particular study will support the conclusions. In the American Legion studies there is sufficient concern with these issues to question the validity of the results of the study and their interpretation. The following discussion will spell out these concerns with the first four reports as they relate to sample selection, representativeness, questionnaire construction, measure of exposure to herbicides and combat, data analysis, and selected outcomes. We will not discuss the utilization study.

SAMPLE SELECTION

The authors chose a cross-sectional sample from American Legion membership roles from six states (CO, OH, MD, PA, IN, and MN). After exclusion of those with 20 or more years of membership, one-seventh of the records were selected at random. Each man in the one-seventh sample was sent a postcard to indicate if he was a Vietnam Era veteran, since this information is not included in Legion membership records. Those who did not return the card (an unspecified proportion) were contacted by the Post Adjutant to identify those known to be non-Era veterans. Vietnam Era veterans and those of unknown status were then contacted by 'volunteer researchers' to determine actual service location, and to encourage participation.

From these papers and a 1985 document,[9] it seems that the sample selection is based on an assumption that about 15% of all Legionnaires are Vietnam-era veterans. From the earlier report, we know that 85,000 men were included in the 1/7th random sample from all 6 states, and that 50,000 returned the postcard indicating time of service. The remaining 35,000 were apparently classified by volunteer researchers. 12,588 men were identified as Vietnam-era veterans and 6810 completed questionnaires. None of the "attrition" in the population is broken down by cohort status.

It appears, however, from statements elsewhere in the papers that there was more to the sampling procedure than this. The authors state that they oversampled Vietnam veterans (taking 15 of each would indeed be slight oversampling of Vietnam veterans), yet their final sample has 42% Vietnam

veterans and 58% non-Vietnam veterans. This is precisely what you would expect without oversampling. The first paragraph of the first paper says that 32%-48% of era veterans served in Southeast Asia.

The authors also say nothing about differential response rates between the two groups. In the Vietnam Experience Study (VES), the Vietnam group was more likely than the comparison group to participate in the study. If there had been also a higher response rate among Vietnam veterans, it is even less clear how the investigators did their sampling. In the VES, we found only one factor that differentially influenced participation rates in the examination component between Vietnam and non-Vietnam veterans. Non-Vietnam veterans with higher education levels were more likely to participate in the examination, perhaps because they understood the importance of their participation.

The preliminary 1985 report of these data[9] raises additional questions. The description of the sampling design differs somewhat from that described in the Environmental Research series of papers, although we believe they are describing the same exact study. This earlier report, however, says the 770 research volunteers were given the names of only those legionnaires who did not return postcards. They were still said to have been given 200 names each. This 1985 report also says that 12,588 men were identified as Vietnam veterans and mailed questionnaires. The 1988 report says that 2858 subjects who served in Southeast Asia returned questionnaires. Since their response rate is reported to be between 52% and 64% for both cohorts combined (Southeast Asia and other), it is difficult to understand precisely what was done.

REPRESENTATIVENESS

The authors admit that they do not have a "representative" sample of Vietnam Era veterans, since American Legion members represent the "solid middle section of white America". Demographic data on the both the total sample and respondents are sketchy, but the authors did indicate that 98% of the participants were white. The authors also indicate that participants have been resocialized sufficiently to join the American Legion.

There are further reasons to doubt that the survey participants were representative of Vietnam veterans:

1. In the Agent Orange Validation Study (AOVS), interviewed veterans who believed they had health problems or were exposed to herbicides were clearly more likely to go for medical exam than those who believed they were in good health or had little exposure to herbicides.[10] It is plausible that the same bias would occur in the American Legion Study in those willing to spend time filling out a long questionnaire.

2. Bias could be introduced by the use of volunteers to determine service location and establish contact. Recruitment of volunteers for assistance may have its place in studies without a strong a priori hypothesis known to the volunteers. In this case, however, the hypothesis is quite clear to the volunteer researchers, to the American Legion, and to the participants. Vietnam veterans with health or psychological problems and non-Vietnam veterans without problems could have selected themselves for the study by returning the postcards. Even more disturbing, the volunteer researchers

could have selectively influenced participation. The researchers were given "goals" to identify 15 Southeast Asia and 15 non-Southeast Asia veterans for the study. With these expectations, it is easy to hypothesize that a well-meaning volunteer could have chosen the "worst" Vietnam veterans and/or the "best" non-Vietnam veterans.

3. The relatively low participation rate could lead to bias and a non-representative sample.

4. The definition of the eligible and final study population is inadequate. The reader should be given the following information: the size of the original total population sampled and the 1/7th random sample; the number of men comprising the one-seventh random sample of members with less than 20 years of continuous membership; the numbers of Vietnam and non-Vietnam veterans to whom questionnaires were sent; the number from this sample who returned postcards, who were ultimately contacted, and who could never be reached in any way and remained status unknown; of those who were contacted, how many participated, how many refused, and how many were lost to follow-up at this stage; and as much of the above as possible should be given by cohort status. With these numbers, one can compute the magnitude of losses and thus provide an assessment of the adequacy of the final respondent sample. The authors do not explain why they used these unorthodox recruitment procedures or why these procedures would not introduce bias in a study of this type.

The authors fail to use standard, accepted methods of presenting data. The extent of the potential bias introduced by this sampling scheme cannot be evaluated, because the authors do not provide baseline demographic information on the original sample and the selected population. Even basic information, such as age distributions by type of service (Army, Navy, etc.), are not provided. Information on at least some veterans, such as place of service, service dates, rank, and discharge status could have been verified from discharge records, yet the authors did not do so. The same holds true of cohort comparisons among respondents. The reader should see, for example, the age, race, education, and income distributions for Vietnam vs. non-Vietnam veterans and also for the different combat cohorts since so many comparisons are made by combat status. This is especially important because so many of their presented analyses are essentially crude and do not control for all these important variables.

The authors could also compare their sample of veterans to veterans from other studies if they want to examine representativeness. They say their study group is 98.5% white; this obviously is not representative of the general population or of the racial distribution found in other veteran studies. They say that their study group is "representative of the solid 'middle section' of white America, with its relatively high educational and income level and marriage rate" (p. 147). This statement may be a little misleading. Compared to other veteran studies that included more non-white veterans,[6,7,8,11] Legionnaires appear to have no more education than the veterans in the CDC study and substantially less than veterans studied by Card. The marriage rate among the Legionnaires may in fact be very nonrepresentative. Using the numbers of "ever-married" veterans (p. 136), the rate of ever married is 68% in both cohorts. This is extremely low; the rate in the VES study is about 91% and in the Card study about 93%.[11]

The authors do report on different response rates by state. On p. 124 they give it as ranging from 52.5% in Pennsylvania to 64.1% in Minnesota. (This is apparently inflated somewhat—bad addresses are removed before calculating the rate.) On p. 179, however, response rates range from 58.1% in Pennsylvania to 64.6% in Minnesota. These data become even more puzzling in Table 4 (p. 125), which shows more total respondents from Minnesota than from Pennsylvania. Since Pennsylvania has three times the population of MN, either the investigators weighted the sample by state or Minnesotans are far more likely to join the American Legion than Pennsylvania veterans.

The authors claim that "representativeness of study subjects is intimately related to their response rates," and then proceed to give us response rates by state instead of by cohort. The total response rate in this study is not good to begin with (about 54%), and if the rate varies significantly by cohort, this could be a serious source of bias. The authors exclude from the denominator of their response rate those questionnaires "returned for bad addresses or otherwise undeliverable." This is very unconventional and will inflate the response rate a little or a lot depending on the number of veterans who could not be tracked down. So, the response rates presented are already inflated by some unknown degree.

In order to address potential bias in representation, the authors compare "the distribution of important variables" between men coming from high-response posts and men from low-response posts in an effort to address the question of representativeness of their sample. Because they did not find differences between these "high-response" and "low-response" subjects for these variables, they conclude that they have little response bias. This is a meaningful analysis only if you make the unsubstantiated assumption that respondents from "low-response" posts are more like non-respondents than respondents from "high-response" posts. The observation that age was related to response rate could, on the other hand, completely explain inter-post differences (i.e, respondents from all posts are similar, but some posts have higher rates of non-response because their membership is older). The authors also suggest that their sample is not biased because reported herbicide and combat levels by posts with high response rates are comparable to those with low response rates, although their outcome data suggest otherwise. Nearly 9% more men from high response posts report excellent health than those from low response posts. This suggests that those with the most health or psychological problems could have been recruited first, with low response posts never getting around to recruiting other veterans. With their low response rates, it is quite possible that socio-demographic differences attributed to Vietnam service may be heavily influenced by differential motivational factors for participation. Finally, the authors try to address bias statistically, but tests of statistical significance probably are not appropriate for assessing selection bias. Such an approach to confounding, on the other hand, is well accepted.[12]

QUESTIONNAIRE CONSTRUCTION

The questionnaire is designed so that information on combat, herbicide exposure, symptoms of post-traumatic stress disorder (PTSD), social factors upon return, and helpfulness of the Veterans Administration were collected before the outcome data. Structuring this questionnaire in this way may bias

respondents to falsely associate exposure with illness. Also, the tone of the questions implies that the veterans did have problems upon return. The herbicide section even includes questions on acute symptoms following exposure, thereby reinforcing to the respondent the potentially harmful effects of exposure.

The use of a self-administered questionnaire has a number of important limitations that could affect the quality of the responses: the respondent can take as little or as much time as he wants to complete the questionnaire; the absence of a trained interviewer precludes the ability to answer clarifying questions and to encourage completion of all questions; and the respondents can ask family, friends, or other veterans for their opinions and help in filling out the questionnaire.

HERBICIDE INDEX

As Lilienfeld recently stated, "It is the assessment of exposure that is the cornerstone of any environmental epidemiologic study ....".[13] Thus, the validity of the findings in this series of papers depends on the accuracy with which exposure was assessed in this study. We reviewed carefully the original paper describing the exposure estimation procedure[14] as well as the summary of exposure estimates for the men in this study. Especially in light of the findings in other publications, the authors of these studies must show that they have overcome the recognized difficulties and obtained valid exposure measures. We believe that their measures are unreliable for the following reasons:

1. Estimates of exposure are based completely on veterans' recollection of their locations and dates of service, without validation from military records.

2. The authors' procedure greatly overestimates the relative exposure of veterans who were more than 1-2 km from known herbicide sprays.

3. The procedure implicitly assumes that the only exposure of concern was from contaminated soil and perhaps water, which may result in a substantial overestimate of exposure for those within 2 km of a documented spray.

4. There were no comments concerning calculation of time periods for which no location was reported.

5. The authors ignore demonstrated limitations in indirect indices for dioxin exposure.

6. The exposure classifications appear arbitrary with no clear biological basis.

The following are detailed comments on these issues:

1. There are several concerns about exposure estimates based on recall not validated by historical records. Both published manuscripts report that exposure was estimated by asking veterans the dates they had served at about 100 locations in South Vietnam. First, because only 73% of Vietnam veterans reported enough location data to estimate herbicide exposure, for all analyses

using this variable, at least 1/4 of the data are missing. Second, it is difficult to remember specific dates and places nearly 20 years after the fact. Third, the questionnaire listed the names of base camps, villages, (along with a small map of Vietnam), yet much of the herbicide exposure may have occurred in more remote areas. Fourth, even with accurate recall of location and time, veterans would have difficulty giving correct exposure information. Veterans would think they were most heavily exposed when walking through defoliated areas, although by that time, the chemical constituents would have decomposed. In contrast, veterans would have been most exposed shortly after spraying and before chemical decomposition, when the jungle looked relatively normal. Using the model developed by the American Legion investigators, it would not be unusual for veterans to preferentially remember time spent in defoliated areas, and with the one-year half-life for herbicide in the environment built into the model, these men would be considered exposed.

For an alternative measure of personal exposures, veterans were asked if they had ever handled herbicides. Veterans could have responded positively if they handled many different types of chemicals, which they now presume were herbicides. Most of the chemicals used near base camps, etc. were insecticides, not herbicides. Thus, the index could represent belief in exposure to Agent Orange rather than actual exposure. In good faith, veterans could think they were exposed because they walked through defoliated areas, and because they sprayed or were otherwise exposed to unknown chemicals. On the other hand, this variable should not be discounted simply because it does not reflect objective exposure. The CDC studies found that reported exposure is associated with many adverse outcomes. The AOVS, however, found no correlation between reported exposure and objective exposure as measured by serum TCDD levels, suggesting that the association between reported exposure and adverse outcome is not due to exposure to TCDD.

The authors report that they obtained adequate data from 73% of the respondents to calculate a score, but they do not define what constitutes adequate. Because of the long half-life the authors used, their exposure measures probably do not depend very much on accurate date information. The VES showed that many soldiers moved frequently. Possibly their data are least adequate for those Army and Marine veterans who moved the most (and might be the most interesting group to study). It would be most adequate for those who remained in one spot for the war. The authors give no information on this. They do say that the entire questionnaire took 45-60 minutes to complete, including health status and feelings about the Veterans Administration, so that veterans could not have taken too long on the map portion. The score reflects where they served in Vietnam and when, which may be a surrogate for occupational specialty and branch of service (i.e., these are potential confounders for herbicide exposure). The results of the AOVS indicate that this exposure score, as well as epidemiologic exposure measures developed by CDC, probably has nothing to do with exposure to Agent Orange.

The authors should have tried to verify veterans' recollection of where they served by validating a sample of questionnaires with military records. Such records were used in the AOVS; they are the dates during which a veteran served in various units (from his military record), and the locations of those units on those dates (abstracted from military records by the Environmental Support Group).[10] In addition, the AOVS showed that there is no relation

between current TCDD levels and relative opportunity for exposure according to a wide variety of scores derived from the military records or from self-reported exposure. Vietnam veterans whose main job was not handling herbicides have tissue TCDD levels similar to unexposed civilians of the same age. Thus, there is no evidence that ground troops who served in South Vietnam had meaningful exposure to TCDD.

2. Simulated Ranch Hand sprays at Eglin Air Force Base, Florida, showed exposure decreasing far more rapidly (as a negative exponential), with negligible exposure more than 1-2 km from the center of the spray path.[15] The exposure measure used in the American Legion study, however, allows for substantial exposure up to 15 km from a spray, with exposure decreasing as the inverse of the distance from the spray. Most perimeter sprays had no more dispersion than did Ranch Hand sprays, since most of the perimeter sprays would have been from ground level or low altitude. In contrast to this new report, for most scores the AOVS used only locations within 2 km of a spray to estimate exposure, a procedure that is in much better agreement with the available data.

In addition, some base camps in South Vietnam were quite large, so that perimeter spraying would not necessarily result in significant exposure for all veterans stationed at that camp. While no details are given, it is possible that each base camp is represented as a point in computing potential exposure in this report. In their 1986 report, the authors show that, for 6 base camps, there are far more herbicide spray "hits" 5-15 km from these base camps than within 5 km.[14] These considerations suggest that the authors may have substantially overestimated herbicide exposure for many veterans, in contrast to their statement that "Computed exposures will thus tend to underestimate true exposures."

3. The exposure measure in the American Legion study assumes a half-life of 1 year for the decay of TCDD in the environment. This is roughly consistent with the experimental data on the half-life of TCDD absorbed to soil and similar to the half-life of 5 years used to compute the "slow" or E_3 score in the AOVS. However, this half-life is about two orders of magnitude longer than the estimated half-life of several days for TCDD on vegetation. The Stellman exposure measure, therefore, assumes that the significant source of exposure is soil and gives an estimated exposure far greater than that which would be obtained if the important source was TCDD on vegetation. In fact, the relative importance of vegetation vs. soil is unknown.

The distribution of their herbicide index basically shows most veterans clustered at the low end with a few scattered out on a long tail. Even if one were to make the assumption that this index (based on HERBS tapes and self-reported location) has any validity, there is still no discussion of what the levels of the index might represent in biological terms. Until and unless some type of method of validation can be applied, the value of any such index is completely unknown. Certainly, past study of epidemiological and biological markers has taught us that and the authors should at least acknowledge the limitations of such markers.

4. There were no comments concerning calculation of scores for time periods for which no location was reported. If these periods were merely assigned a zero, than the analysis should have been adjusted for the number missing days.

Otherwise results could be biased: men who report more illnesses might also report locations for more days, receive a higher score, and artifactually create the impression of an associations between health outcomes and herbicides.

5. The half-life of TCDD in humans has been estimated at 7.1 years (95% confidence interval 5.8 to 9.6 years) which means that only 2-3 half-lives have elapsed since the Vietnam War.[4] Measurements in Ranch Hand Veterans have demonstrated that selected veterans who were exposed to Agent Orange in Vietnam have measurable and quantifiable serum TCDD levels which are above background levels.[16] When the same serum TCDD measurements were made on ground troops who were classified as highly exposed by any one of five exposure indices including self-reported exposure, the supposed highly exposed group had a distribution of serum TCDD levels almost identical to veteran controls with no Vietnam experience.[17] The large set of data on Vietnam veterans in the AOVS with a variety of exposures has established the serum TCDD measurement as the current preferred method of assessing TCDD exposure in Vietnam veterans.

6. The criteria for "high," "medium," and "low" exposure classifications were not given. However, from the frequency distribution (p. 120) and numbers in the tables (pp. 158-159) it appears that "high" included anyone with an exposure level at or above the mean, i.e. 0.36-1.60. That means that, with the unreliability of the question responses, there was probably little difference between the "medium" (0.10-0.36) and "low" (0.0-0.10) groups.

Of note, the U.S. Air Force formulated an Agent Orange exposure index for Ranch Hand veterans, based on excellent records of the actual activities of the Ranch Hand veterans during their tours of duty. After comparing their index with measured serum TCDD levels on a subset of Ranch Handers, the Air Force decided the index was inadequate and that they should obtain a serum TCDD level on each of the Ranch Hand veterans. The blood samples have already been collected and the analyses are in progress. It is discomforting, therefore, that the authors describe their system as the gold standard, while referring to others as "yet to be validated exposure methods such as analysis of dioxin residues in tissue collected some 15 years postexposure".[11]

COMBAT INDEX

In their studies the American Legion investigators used a self-reported combat scale analgous to the one used by CDC. Their computation of an herbicide exposure opportunity index was based on the same sets of spray data used by CDC, and their OE3 formula is analogous to the E2 score used by CDC in its TCDD validation study in III Corps area veterans. The main methodologic difference was that in their questionnaire each veteran was given an annotated Vietnam map, with place names and military unit names, and was asked to recall and record his location by month and year. With time limited to month, they were forced to use the assumption of a rather slow TCDD decay curve in their OE3 formula. In its TCDD study CDC used military records to identify the unit and probable location of each veteran for each day, thus allowing the use of both rapid and slow decay models for separate analyses.

The combat index used does not give sufficient detail to serve as a major exposure variable. The study includes groups other than ground troops, but focuses only on ground troop experience. For instance, fixed wing pilots or medical personnel could have had traumatic combat-related events, that are not described by this index. The combat index has limitations, even if it is confined to ground troop experience. The questions are redundant, and their intent is unclear. For instance, shooting one Vietnamese could elicit a response to 5 of the 8 questions. The index focuses on frequency not intensity. Seeing a dead man on five separate occasions could get more weight than being involved in one large ambush. The scoring procedures are also not weighted according to the severity of the experience. For instance, finding yourself in a situation you thought you would never survive receives equivalent weight as firing your weapon or seeing dead enemy. None of the combat indices, including the one used in the VES, are ideal but since combat is their major exposure of interest, they could have asked a more extensive battery of questions rather than a screening battery.

There were inconsistencies regarding the number of veterans in various combat classifications. On page 119, for example, it was stated that 2087 Southeast Asia veterans had combat scores. However, on page 160 the total number of Southeast Asia veterans with combat scores was 2845, a number which apparently did not include herbicide handlers. This is unlikely since the total number of Southeast Asia veterans who were not herbicide handlers was only 2858 - 102 = 2756.

Some of their conclusions based on these indices are open to question. Higher combat score correlates with lower income. Yet, given the cross-sectional nature of the data, it is impossible to distinguish cause from effect. The authors conclude that "significant family income loss has occurred among Vietnam combat veterans", but possibly those with lower income for whatever reason are more likely to score something as "very often" rather than "rarely, sometimes, or often". The finding of higher separation and divorce rates among the high combat group could be attributed to the same circular logic. In this section an observation that seems to reflect the authors bias is that divorce rates were 4 times as high in the high combat group as in the non-Vietnam group, although the percentages given, 60.4% vs. 28.4% (p. 136) do not reflect this.

The herbicide and combat indexes are correlated, and the herbicide index drops out in some multivariate analyses. Because of the resulting multicollinearity, the standard errors on the coefficients (not given) would be quite large. Although the resulting coefficients may be significantly different from zero, they are unlikely to be significantly different from each other. Therefore, their relative "importance" would be difficult to assess. Further, because of the instability of these estimates, these kinds of regressions often change radically when more subjects are added to the analyses. In addition, if combat is subject to misclassification, and combat leads to certain health outcomes, then residual confounding may exist even after adjustment for the combat score. Thus, residual confounding could account for apparent association between exposure to herbicides and adverse health outcomes, each after adjustment using the combat score. The finding of correlation of both indices with self reports of physical and reproductive health problems is consistent with the VES. In the VES, however, these results were found on the interview component and almost never substantiated by the physical and laboratory exam.

There are two potential sources of bias with these analyses that the authors do not acknowledge or address. Because the combat index relies on self-reported data, it may not reflect actual combat; we know only that it reflects perceived combat, and the data should be analyzed and interpreted in that light. Second, even if the combat index validly reflects combat, the men who saw more combat may have been different going in than the men who saw little or no combat. The Louis Harris study of attitudes toward Vietnam era veterans found that "among those who served in Vietnam, those with less than high school educations at induction were three times as likely to see heavy combat at were those with college educations".[18] They concluded that "combat assignment processes ... served to mirror the underlying class discrimination of the society itself". If this is the case, then many of the socio-demographic, behavioral, and health differences seen by combat status in the American Legion study may be due to preexisting differences in the men who saw different levels of combat. This issue could have been better addressed by more adequate control for all available covariates in the analyses. The general lack of specificity associated with combat (i.e., it is related to almost every reported health outcome) increases the likelihood of a reporting or selection bias.

The three combat exposure groups and the three herbicide exposure groups may differ appreciably with respect to other characteristics that are associated with reporting of outcomes. For example, Navy and Air Force veterans make up about 49 percent of the Low combat exposure group but only 10 percent of the High exposure group (Table 3 and Figure 5). Although not shown, the military rank profile of these exposure groups could also be quite different. Both branch of service and military rank could be important correlates of outcome reporting and should have been taken into consideration in comparisons among the combat and herbicide exposure groups. Other baseline traits that would be important to take into consideration are military occupational specialty and whether a man was drafted or volunteered for military service. Another point that should have been addressed is the possibility of response bias or selective reporting of outcomes by Vietnam veterans. Further, it is not possible from a cross-sectional study that relies on self-reported exposures (particularly combat) and self-reported outcomes to establish with certainty whether the exposure led to the outcome or vice versa.

ANALYTIC STRATEGY

There are several points of concern in the analysis:

- Crude associations are reported in most instances. Joint effects of combat and herbicide exposure were assessed (and hopefully the 'non-significant' main effect of herbicide exposure was left in the model with and herbicide-combat cross-product term), but collected data on demographic variables or smoking, drinking and drug use were not included in multivariate models.

- dates during which the study was conducted were not given.

- the possibility of residual confounding of the association between the herbicide index and various health outcomes by combat, age, etc., does not appear to be fully appreciated.

- power calculations leading to choice of sample size including the achieved power for various prevalences are not given. Is power for herbicide exposure clearly better than the Air Force Ranch Hand Study, where there are clearly exposed and unexposed groups?

- No mention is ever made of missing data and how they are handled. Since the numbers are not consistent throughout the papers, the authors appear to have chosen to ignore this issue in the analyses. Depending on the extent of missing data, this could represent a real bias. For example, the analysis of average weekly consumption of alcohol is based on 1824 (64%) non-Vietnam veterans and 3254 (83%) Vietnam veterans. Because of a substantial amount of missing data and a large difference between the two cohorts, the validity of any comparison is questionable. For many outcomes, numbers are not given so no estimate of missing data can be made.

- The authors classify persons as "In-Country" or not. There is no discrimination as to how long they were "In-Country" and no controls for this factor in any of the analyses in this report. A related problem is the use of birth year for analyses, not year of service in Vietnam. As we know from VES, the age of the veteran at time of service, and the actual year in which that service occurred were important factors in all of the analyses. The American Legion investigators confound both of these issues in their design.

- The data did not demonstrate "that sufficient numbers of troops are available and identifiable for epidemiologic study of herbicide effects". This statement is a leap of faith from very limited and questionable exposure data. From Figure 3 (p. 120) it appears (assuming their herbicide exposure index is measuring exposure) that there might be insufficient numbers of men with high exposure scores.

- The authors say that the "internal consistency of the findings also lends credibility to the study". However, nowhere do they present data that support what is really meant by internal consistency (i.e., that a particular association is present in various subgroups of the total study group). By internal consistency, the authors seem to mean that there was a large number of positive exposure-response associations for combat and herbicides. This is circular reasoning, using the health outcome results to justify the validity of the exposure measures.

- While the findings in Table 1 (p. 156) are consistent with the results of the VES telephone interview component, results for the infrequent conditions should have been tabulated for descriptive purposes and for completeness. Also, all conditions should be shown, not just those that were reported more frequently in the Vietnam veterans.

- Why would herbicide handlers have the highest mean combat score in view of their job distribution in Table 2 (p. 121)?

- There is no discussion of why the herbicide handler group does not show an excess of adult acne (OR = 0.99) whereas the High herbicide exposure group does show an excess for this condition (OR = 1.45) (Tables 2,3).

- There is no discussion of the curious finding that "benign fatty tumors" is the only reported condition that is positively associated with both combat and herbicide exposure.

- Despite the large number of statistical tests presented, the authors fail to discuss the problems of multiple comparisons in the same data set.

- Psychological scales: Most scales chosen represent general adjustment and not specific diagnoses. The scales are all said to be reliable (e.g., repeatable), but they do not provide documentation of their reliability or any discussion of their validity.

- The authors should have pointed out that the correlations obtained, while statistically significant, are weak (Tables 6 and 8).

- There is a tendency of the authors to downplay, not to recognize, or to ignore the limitations of this study and to make only selected references to available knowledge in the literature such as the VES and the AOVS.

FINDINGS

Both the American Legion studies and the CDC studies found that self-reported combat exposure and self-reported or computed herbicide exposure opportunity are correlated, and that combat exposure correlates with subsequent anxiety, depression, post-traumatic stress syndrome, and certain self-destructive behaviors. In other words, we agree that combat tends to leave long-lasting "invisible wounds." Furthermore, both sets of studies found that combat-exposed people (often also believing that they were exposed to herbicides) tend to report more physician visits and more "yes" answers to a wide variety of symptoms and illnesses, including more miscarriages for their wives. Because of its larger budget, CDC was able to seek objective confirmation of some of the subjective data. Upon physical examination and laboratory tests, most of the differences between the Vietnam and non-Vietnam groups disappeared. Further, CDC found low residual TCDD levels (used as a marker of prior herbicide exposure) in the Vietnam veterans, not different from the levels found in the non-Vietnam group. Among the Vietnam veterans, there was no correlation between TCDD levels and either self-reported herbicide exposure or exposure opportunity scores calculated several ways.

High residual TCDD levels are being found by CDC's laboratory, however, in Air Force Ranch Hand veterans exposed occupationally, in civilians who are former herbicide production workers, in people with heavy environmental exposures in Missouri, and in people who were heavily exposed to the fall-out of an explosion in a herbicide factory in Italy. This last group has residual TCDD levels several orders of magnitude higher than the highest level found either in the CDC studies or in Vietnam veterans studied by the New Jersey group, yet after 12 years chloracne is the only ill-effect seen so far in the Italian group.[19]

Reproductive outcomes. The reproductive findings are confined to ever-married men born in 1940 or later. The restriction on birth year is done in an attempt to "eliminate reproductive experiences that occurred before the Vietnam era". This is a very crude way to accomplish this goal and is subject to significant misclassification. Many children with no opportunity for "exposure" will be included and others who were conceived after service will be eliminated. In order to obtain meaningful results the investigators must have the veterans' dates of service and the dates of the reproductive events; all children and pregnancies should be included or excluded based on these dates, not on the birth year of the veteran. The authors found that Vietnam veterans reported more difficulty having children than non-Vietnam veterans, but both cohorts reported fathering the same average number of pregnancies. These results are similar to those of the VES.

The analysis of miscarriages is very difficult to evaluate because only a subset of veterans are included in the analysis. The report starts out with 5097 veterans who were ever-married and born 1940 or later. However, the miscarriage data are based on 6622 "birth outcomes" reported by 2950 veterans. There is no explanation why over 40% of the eligible veterans have been excluded from the analysis. The Table 10 (p.166) note says that the restrictions on the veterans now include discharged 1974 or earlier, with the first pregnancy reported subsequent to discharge, but there is no explanation of why these restrictions are needed or how many men were lost from each cohort through the application of these restrictions. Thus, their data show a great deal of underreporting of this event in both cohorts (as did the VES data and most data that are based on fathers' reports). Clearly, there was a great deal of underreporting. Both the retrospective nature of the study and the fact that most of the reports may have been proxy reports would have affected the underreporting. Veterans who have no reason to suspect reproductive problems as a result of their previous military experience are likely to forget more miscarriages of their wives than the Vietnam veterans. Because of these limitations, one cannot be expected to comment responsibly on these findings because they are based on what is clearly a small subset of the total study group other than to say that rates of miscarriage in the general population are in the range of 20%-25% of all pregnancies, far higher than the 7.6% and 5.5% rates found in the American Legion Study for Vietnam and non-Vietnam veterans, respectively.

Social and Behavioral Consequences. The general items that were used to assess social and behavioral outcomes (pp. 132-133, and actual questionnaire were reviewed) are very limited. Generally, they represent symptom ratings. Only a few are time linked (within the last 6 months). Although some of these probably would correlate with more standardized and valid psychological instruments, one would expect that their validity would be more limited than the standardized tests due to the limited number of items (even though they have reasonable reliability). The fact that all of the variables are highly intercorrelated suggests that these different scales are not really measuring different factors, but probably are measuring general "psychological distress" (p.139). This has been a problem for the scale that much of this has been taken from, the Psychiatric Epidemiological Research Interview. These measures do not provide a DSM-III diagnosis since the DSM criteria and methods were not used in the study. Given that the symptoms are never time-linked, a subject could have had one symptom this year, another last year, and another 5 years ago and ended up with a high score.

The interpretation of some of the findings are questionable. For example, the authors state that "the correlation is comparatively strong with combat exposure". Given that one is $r = 0.18$, the other $r = 0.30$, accounting for less than 2% and 9% of the predicted variance, these are unimpressive correlations. In Table 5 (p. 141), there is no correlation with combat exposure over 0.30, most are under 0.22. The Agent Orange index correlations are even lower. The mean differences between groups in Table 6 (p.141) are also of limited clinical meaning, although statistically significant given the large sample sizes. It is misleading to suggest that the Vietnam veterans are more psychologically distressed than the non-Vietnam veterans, since these score differences are minimal (1 point generally out of 20 possible). The graphs on page 142 (Fig.6) seem distorted given that the correlations are all less than 0.30.

It is of concern that the authors never look at the relationship between well recognized risk factors for psychological symptoms such as drinking and smoking and any of the psychological data. Instead, they conclude that the psychological problems are caused by the Vietnam experience, as are the drinking and drug problems when it is known that the psychological and drinking problems are highly interrelated and may account for more of the current findings than anything else.

Post traumatic Stress Syndrome (PTSD). The main concern is the diagnosis of PTSD. First, the multiple approach to combat exposure classification is crucial. The authors assume that any subject who had a high combat exposure score had exposure to a traumatic event, as required by the PTSD criteria. This is not always accurate, as people working on transportation details may have seen many dead bodies, but never have been in life-threatening situations or had been traumatized. PTSD rates depend on the combat exposure index, which of course is correlated with PTSD symptoms. There is circularity to this approach to this disorder's definition. The authors use a symptom checklist without time frame (viz., date of discharge from service); no DSM-III diagnosis is made without a timeframe for symptom co-occurrence. In addition, the authors fail to diagnose other disorders whose symptoms may be similar, if not identical (anxiety disorders, depression, substance abuse, etc.). Therefore, there is no way to identify just those veterans who had PTSD, when they had it, or what else they may have also had. Other traumatic events in the veterans lives are ignored, and it is not clear what "often" and similar words may have meant to a particular veteran. In short, this approach cannot provide a DSM-III PTSD diagnosis. At best, it provides a group of symptom ratings (p.182) over a number of years (different for different veterans).

On page 183, the investigators use mean values of PTSD symptoms. This is not meaningful when one recognizes that one veteran may score 4-5 points on 5 symptoms over a 15-year period and get a score of 20, while another veteran may score rarely (2 points) on 10 symptoms over the past month and also get a score of 20. These men are not likely to have psychological problems. One is more concerned with the second rather than the first in some instances; yet, the authors treat both of these men as identical in their analyses.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date . November 28, 1988

From Chief, Agent Orange Projects, OD, CEHIC, (F16)

Subject Comments on the Vietnam Experience Studies of Stellman, et al.

To Stephen B. Thacker, M.D., M.Sc., Assistant Director Science, CEHIC, (F29)

These papers are a bit sloppy (data reported in one part are not consistent with that reported in another), but they probably do report accurately the results of the survey. The authors do not report well the potential sources of bias. They overgeneralize their conclusions and in some cases draw conclusions opposite to those I would draw about the generalizability of their results. They also provide little detail on the way their sample was drawn. In addition, they ignore other research of which they are certainly aware (AOVS in particular).

It is not possible to pronounce on the details of their sample selection scheme, because the details are not given. They have subsampled members of the American Legion (AL) in 6 states. Although they state that the AL has 700,000 era veterans, "a meaningful percentage of those approx. 3-4 million men who served in the military during that era" (p. 113), they also state that 9 million men served in the era (p.112) of whom 3-4.4 served in SE Asia. These statements are inconsistent. I believe the membership is 700,000 out of 9 million, or about 8% of era veterans. They note that membership is mostly white. They state that AL members are more stable than nonmembers who are veterans and that therefore, physical and mental health problems would be worse in a larger sample. This is opinion. It could also be argued that AL members are less comfortable in the general social atmosphere and therefore join groups of old military vets because they have more scars from their past service and more trouble adjusting to the world at large.

It is not clear how they subsampled the veterans. Unfortunately, they give some information on further sampling procedures, but no numbers to determine how many people dropped out at each stage. They eliminated a percentage of non era veterans if they returned a postcard indicating whether they were era or non era, but do not say how many did or did not complete this step. They then sent the remainder of the names to individual posts of the AL to have post secretaries decide who was or wasn't an era veteran. Members of the AL, termed volunteer researchers, were then given lists of about 200 names, including those known to be era veterans plus those not known to be either era or non era by either of the above two steps (return of postcard or knowledge of post secretary). This selection technique looks OK so far (save that they're all AL members), except for the absence of numbers on how many fell into each group. The volunteer researchers were trained by Stellman and Stellman to identify 15 who served in SE Asia and 15 who did not from their list of 200. This is where I begin to get worried about the sample design.

Surely the volunteer researchers knew the study was to look at the health effects of Vietnam service and AO exposure. They may have volunteered because they had media generated opinions on the outcome of the study. If they only had to identify a total of 30 people out of a list of 200 (not all of whom were actually era veterans), they would most likely have stopped their effort when they got to 15 in each group. Perhaps they contacted first those people they were personally acquainted with. Perhaps a higher percentage of these had preformed opinions of the health effects of the Vietnam war.

It appears, however, from statements elsewhere in the papers that there was more to the sampling procedure than this. They say they oversampled Vietnam veterans (taking 15 of each would indeed be slight oversampling of Vietnam veterans), yet their final sample is 42% Vietnam and 58% non-Vietnam. This is precisely what you would expect without oversampling (and not what you'd get from 15 of each). The first paragraph of the first paper says that 32-48% of era veterans served in SE Asia. They also say nothing about differential response rates between the two groups. In our study, the Vietnam group was more likely to travel to Abq. than the comparison group. If this research team also had a higher response rate among VN vets, it is even less clear how they did their sampling.

Report #1, the 1985 report on the same studies produced as an American Legion document, raises additional questions on the sampling. It appears to be reporting on the exact same study, but describes it differently. We are here given the information that 50,000 postcards were returned indicating war era. However, this earlier report says the 770 research volunteers were given the names of only those Legionnaires who did not return postcards. They were still said to be given 200 names each.

This 1985 report also says that 12,588 men were identified as "Vietnam veterans" and mailed questionnaires. The 1988 report says that 2858 subjects who served in SE Asia returned questionnaires. This is not consistent with the response rate reported as between 52% and 64% for both cohorts combined (SE Asia and other).

They do report on different response rates by state. On p. 124 they give it as ranging from 52.5% in Pa to 64.1% in MN. (This is apparently inflated somewhat--bad addresses are removed before calculating the rate.) On p. 179 it's 58.1% in PA to 64.6% in MN. Table 4, p. 125 also shows more total respondents from MN than from PA. PA has three times the pop. of MN. Either they weighted the sample by state or Minnesotans are far more likely to join the AL.

The rest of the report also discusses only VN versus other. They never again use the category SE Asia, so I can't tell which they were actually looking at. They also never again mention branch of service (after p. 122). This seems a serious omission.

What they have so far is a sample with a high degree of self selection and an obviously high potential for bias on exactly the outcomes of interest.

The first sentence of the discussion of p. 123 indicates the bias on the part of the authors: "The data presented here once again confirm the massive use of herbicidal agents in Vietnam." The data presented have nothing to do with that issue. All they have done is describe their sample selection and given some hints about their AO exposure scale and their combat scale. All herbicide use data is borrowed from documents published long ago.

The AO exposure classification system.

This system is described to some extent in the 1986 publication. It relied on the vet sending back a map of VN with 98 places at which he could indicate his dates of service. They say they got adequate info back from 70% to calculate a score, but they don't define what constitutes adequate. That's a lot of recall unless most individuals spent their entire tour in one location. We know from our study of army ground troops, that many moved frequently. Possibly their data is least adequate for those army and marine veterans who moved the most (and might be the most interesting group to study). It would be most adequate for those who parked in one spot for the war. They give no info on this. They do say that the entire q'aire took 45-60 min. to complete, including health status and feelings about the VA, so they didn't take too long on the map portion. Their scoring system has both a proximity and a time component. What it probably serves as is a measure of where they served in VN, which may be a surrogate for occupational specialty and branch of service. The AOVS would indicate that it probably has nothing to do with AO exposure. The authors take the extreme position of standing logic on its head (p. 127) and describe their system as the gold standard, while referring to others as "yet to be validated exposure methods such as analysis of dioxin residues in tissue collected some 15 years postexposure".

The Combat index.

On p. 179, you find their combat exposure index in Table 1. There's nothing inherently wrong with it except that it's very subjective. The difference between seeing someone killed rarely (score 2) or very often (score 5) is in the eyes of the beholder. Their recall of these events and classification of them between rarely and very often may be highly biased by their subsequent feelings about the war, physical health, and mental health. It would almost certainly be linked to their answers to the PTSD questions. Which came first would be a hopelessly muddled question.

Some of their conclusions based on these indices are open to question. Higher combat score correlates with lower income. They conclude (p. 135) that "significant family income loss has occurred among VN combat veterans". Well, maybe, but then maybe those with lower income for whatever reason are more likely to score something as very often rather than rarely, sometimes, or often. They also find higher separation and divorce rates among the high combat group. Same possibly circular logic. They also say that divorce rates were 4 times as high in the high combat group as in the non VN group. How 60.4% is four times 28.4% (p.136) is something I do not understand.

They also attempt to look at their AO index and combat index as separate variables. They do find they are correlated, and that usually the AO index drops out in multivariate analysis. This is not a surprise. The combat index probably measures very closely the same thing as the sexual satisfaction, skin rash index, whereas the AO exposure index more closely measures branch of service, type of unit, and location in VN.

They also find some correlation with both indices and various self reports of physical and reproductive health problems. These are also not a surprise. They are not at all out of line with what we found in the VES (without an AO exposure index) in terms of either symptoms mentioned or odds ratios. However, we found these results on the interview component only. They were almost never substantiated by the physical and laboratory exam. The synthesis chapter of the VES monograph (Chapter 14) discusses our findings in this regard. Symptoms of four health problems correlated well with self reported herbicide exposure (mapping index was not used), but signs of the the same four problems did not (p. 13). The same was true of the correlation with self reported combat exposure (p.15-16).

Summary

The combat index probably has something to do with combat. It is shown to be highly correlated with branch of service. It would be nice to see their results within Army only. However, combat index is subjective enough that this subjectivity alone could easily explain the entire correlation with physical and mental health and social outcomes.

The AO exposure index would be more interesting if we hadn't already published the AOVS. I agree that the individual could not have deliberately scored himself high for AO exposure. However, their index is serving as a surrogate for something else that related to their Vietnam service, not their exposure to Agent Orange. This something else is in return related to their reported health outcomes, although not particularly independently of their combat index. Again, it's probably a branch of service and occupational specialty index with a definite correlation to combat of its own.

Because there is no attempt to verify any of the questionnaire responses, you're basically back at square 1. The results of the VES fairly convincingly found that VN vets report more adverse health outcomes than comparison vets, but that these are not substantiated by physical or laboratory exam.

All of this, coupled with their sampling of a self selected group means that this study adds nothing to our knowledge of this issue. This is the type of research that launched the concerns about Vietnam service and Agent Orange exposure. It is many years out of synch with current efforts.

Edward A. Brann

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date December 20, 1988

From Epidemiologist, Birth Defects and Genetic Diseases Branch, BDDD (F-37)

Subject Review of Stellman & Stellman Vietnam Veteran Study

To Stephen B. Thacker, M.D.
Assistant Director for Science, CEHIC (F-29)

Explanation of Study Population:

pg. 114 The definition of the eligible and final study population is inadequate. The reader should be given the following information: the size of the original total population sampled and the 1/7th random sample; the number from this sample who returned postcards, who were ultimately contacted, and who could never be reached in any way and remained status unknown; of those who were contacted, how many participated, how many refused, and how many were lost to follow-up at this stage; as much of the above as possible should be given by cohort status.

From what I've been able to piece together from these papers and an earlier document, it seems that the sample selection is based on an assumption that about 15% of all Legionnaires are Vietnam-era veterans (maybe they got this from their pilot study in South Dakota). From an earlier report, we know that 85,000 men were included in the 1/7th random sample from all 6 states, and that 50,000 returned the postcard indicating war era. The remaining 35,000 were supposedly classified by volunteer researchers. 12,588 men were identified as Vietnam-era vets and 6810 completed questionnaires. None of the "attrition" in the population is broken down by cohort status.

Why were these particular 6 states chosen for study? Some explanation is needed.

Possible Sources of Bias:

pg. 124 The authors claim that "representiveness of study subjects is intimately related to their response rates," and then proceed to give us response rates by state instead of by cohort! The total response rate in this study is not good to begin with (54% by my calculation) and if it varies significantly by cohort, they could easily have a serious source of bias operating.

They exclude from the denominator of their response rate those questionnaires "returned for bad addresses or otherwise undeliverable." This is very unconventional and will inflate the response rate a little or a lot depending on the number of vets who could not be tracked down. So, the response rates they are presenting are already inflated by some unknown degree.

pg. 124-125 They conduct a strange comparison of "the distribution of important variables" between men coming from high-response Posts and men from low-response posts in an effort to address the question of representativeness of their sample. Because they did not find differences between these "high-response" and "low-response" subjects for these variables, they conclude that they have little response bias. This is a meaningful analysis only if you make the assumption that respondents from "low-response" posts are more like non-respondents that respondents from "high-response" posts. I know of no reason why this assumption should be true. They say that age was related to response rate; this variable alone could completely explain inter-post differences (ie. respondents from all posts are similar, but some posts have higher rates of non-response because their membership is older).

Some of the standard things they could have done to address bias and representativeness, they did not do. Any information they have available about nonrespondents should be presented to the reader. They mention almost anecdotally that age was related to response rate (pg. 125). Do they know anything else about nonrespondents? Why isn't the age distribution of respondents and nonrespondents compared? Why isn't the cohort (VN+, VN-) distribution of respondents and nonrespondents compared? These are standard, accepted methods of presenting data. The same holds true of cohort comparisons among respondents. The reader should see the age, race, education, income, etc. distributions for VN+ vs. VN- and also for the different combat cohorts since so many comparisons are made by combat status. This is especially important because so many of their presented analyses are essentially crude and do not control for all these important variables.

The authors could also compare their sample of veterans to veterans from other studies if they want to examine representativeness. They say their study group is 98.5% white; this obviously is not representative of the general population or of the racial distribution found in other veteran studies. They say that their study group is "representative of the solid 'middle section' of white America, with its relatively high educational and income level and marriage rate" (pg. 147). This statement may be a little misleading. Compared to other veteran studies that included more non-white veterans (CDC's VES Studies and Card's Lives After Vietnam), the Legionnaires appear to have no more education than the CDC veterans and substantially less than Card's veterans. The marriage rate among the Legionnaires may in fact be very nonrepresentative. Using the numbers of "ever-married" veterans given on pg. 136, I calculated the rate of ever married to be about 68% in both cohorts. This is extremely low; the rate in the CDC study is about 91% and in the Card study about 93%. (This very low marriage rate is difficult to evaluate with certainty because different numbers of ever-married vets - restricted to those born after 1940 -- are given on pg. 163 and are larger than those given on pg. 136 -- they should be smaller because of the additional year of birth restriction).

Missing Data:

No mention is ever made of missing data and how it is handled. Since the numbers keep changing throughout the paper, my best guess is that they just ignore this issue in the analyses. Depending on the extent of missing data, this could represent a real bias. For example, the analysis of average weekly consumption of alcohol (pg. 145) is based on 1824 (64%) VN+ veterans and 3254 (83%) VN- veterans. This represents a substantial amount of missing data in total and a large difference between the two cohorts. The validity of such a comparison is in question. For many outcomes, numbers are not given so no estimate of missing data can be made.

Herbicide Exposure:

pg. 116 73% of VN+ vets gave enough (self-reported) location data to be classified as to agent orange exposure. Consequently, for all analyses using this variable, at least 1/4 of the data are missing.

pg. 120 & 126 The authors present the correlation between the spraying activities and the military buildup in Vietnam as a finding of their study. This correlation is well documented; no study was necessary to detect it. As we have found, this does not necessarily imply that a great number of men actually incurred a biologically meaningful exposure.

pg. 120 The distribution of their agent orange exposure index basically shows most vets clustered at the low end with a few scattered out on a long tail. Even if one were to make the assumption that this index (based on Herbs tapes and self-reported location) has any validity, there is still no discussion of what the levels of the index might represent in biological terms. Until and unless some type of method of validation can be applied, the value of any such index is completely unknown. Certainly past study has taught us that, and the authors should at least acknowledge it.

Combat:

The authors analyze most of their data by level of combat within Vietnam service where combat is defined by self-reports. There are two problems and potential sources of bias with these analyses that the authors do not acknowledge or address. First and most obviously, because it relies only on self-reported data, the combat index may not validity reflect actual combat; we know only that it reflects perceived combat, and the data should be analyzed and interpreted in that light. Second, even if the combat index validly reflects actual combat, the men who saw more combat may have been different going in than the men who saw little or no combat. It makes sense that officers would see less combat than enlisted men and that older men would see less combat than younger men. But, since their data are never controlled for rank and rarely for age, we do not know if these variables might explain differences

now attributed to combat. The Louis Harris study, Myths and Realities: A Study of Attitudes Toward Vietnam Era Veterans, found that "among those who served in Vietnam, those with less than high school educations (at induction) were three times as likely to see heavy combat at were those with college educations". They concluded that "combat assignment processes ... served to mirror the underlying class discrimination of the society itself". If this is the case, then many of the sociodemographic, behavioral, and health differences seen by combat status in the Legionnaires study may be due, in whole or in part, to basic preexisting differences in the men who saw different levels of combat. This issue could have been better addressed by more adequate control for all available covariates in the analyses and through discussion. The general lack of specificity associated with combat (ie. it is related to almost everything) increases the likelihood of a reporting or selection bias.

Reproductive Outcomes:

pg. 162 The reproductive findings are confined to ever-married men born in 1940 or later. The restriction on birth year is done in an attempt to "eliminate reproductive experiences that occurred before the Vietnam era". This is a very crude way to accomplish this goal and is subject to significant misclassification. Many children with no opportunity for "exposure" will be included and others who were conceived after service will be eliminated. They must have the veterans' dates of service and the dates of the reproductive events; all children and pregnancies should be included or excluded based on these dates, not on the birth year of the veteran.

pg. 164 They found that VN+ veterans reported more difficulty having children than VN- veterans, but both cohorts reported fathering the same average number of pregnancies. These results are similar to ours.

pg. 164-166 The analysis of miscarriages is very difficult to evaluate because only a subset of veterans are included in the analysis. We start out with 5097 veterans who were ever-married and born 1940 or later (pg.163 Table 9). However, the miscarriage data are based on 6622 "birth outcomes" reported by 2950 veterans (pg. 164). There is no explanation why over 40% of the eligible veterans have been excluded from the analysis. The Table 10 (pg.166) note says that the restrictions on the veterans now include discharged 1974 or earlier, with the first pregnancy reported subsequent to discharge, but there is no explanation of why these restrictions are needed or how many men were lost from each cohort through the application of these restrictions. I cannot comment on these findings because they are based on what is clearly a small subset of the total study group other than to say that true rates of miscarriage are in the range of 20% of all pregnancies. Thus, their data show a great deal of underreporting of this event in both cohorts (as did our data and most data that are based on fathers' reports).

Eugenia E. Calle, Ph.D.

Jeanne Calle

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date December 5, 1988

From Pierre Decouflé, Sc.D., Epidemiologist,
Developmental Disabilities Branch (F-37)

Subject Review of papers by Stellman & Stellman on health of Vietnam veterans published in December, 1988 issue of Environmental Research

To Stephen B. Thacker, M.D., Assistant Director for Science,
Center for Environmental Health and Injury Control (F-29)

General Comments:

1. Representativeness of the population from which the study group was selected - Are members of the American Legion representative of any larger population of Vietnam veterans, let alone all Vietnam veterans?

   There are no data given in the papers that address this issue, except the statement that the approximately 700,000 Vietnam era veterans in the American Legion constitute a "meaningful" percentage of the approximately 3 to 4 million men who served in the military during that era.

2. Selection of study sample

   It is difficult to judge the adequacy (validity) of the final respondent sample because several key numbers were not given. These are as follows:

   - the number of men comprising the one-seventh random sample of members with less than 20 years of continuous membership.
   - the number of Vietnam era veterans in the one-seventh random sample.
   - the number of veterans in the one-seventh random sample that could not be classified as to era.
   - the numbers of Vietnam and non-Vietnam veterans to which questionnaires were sent.

   With these numbers, one can compute the magnitude of losses and response rates and, thus, assess the adequacy of the final respondent sample.

3. Representativeness of final respondent group

The authors could at least have compared selected demographic and socioeconomic characteristics of their respondents with those of other groups of Vietnam era veterans so that one could assess the adequacy of their study group. The authors do state that their group is 98.5% white, for example, which is very different from the racial composition of every other group of Vietnam era veterans that has been studied.

4. Relationships between combat exposure and outcomes and herbicide exposure and outcomes

There are at least two important points about these exposure-response analyses that the authors do not address. One is the possibility that the three combat exposure groups and the three herbicide exposure groups differ appreciably with resect to other characteristics that are associated with reporting of outcomes. For example, Navy and Air Force veterans make up about 49 percent of the Low combat exposure group but only 10 percent of the High exposure group (based on data from Table 3 and Figure 5 on p. 122). Although not shown, the military rank profile of these exposure groups could also be quite different. Both branch of service and military rank could be important correlates of outcome reporting and should have been taken into consideration in comparisons among the combat and herbicide exposure groups. Other baseline traits that would be important to take into consideration are military occupational specialty and whether a man was drafted or volunteered for military service. The second point that should have been addressed is the possibility of response bias or selective reporting of outcomes by Vietnam veterans. Further, it is not possible from a cross-sectional study that relies on self-reported exposures (particularly combat) and self-reported outcomes to establish with certainty whether the exposure led to the outcome or vice versa.

5. Use of a self-administered questionnaire

This mode of data collection has a number of important limitations that could affect the quality of the responses, such as:

- a respondent can take as little or as much time as he wants to complete the questionnaire

- absence of a trained interviewer precludes the ability to answer clarifying questions and the ability to encourage completion of all questions

- respondents can ask family, friends, or other veterans for their opinions and help in filling out the questionnaire.

Specific Comments (keyed to page numbers of journal)

1. p. 112: What is the basis for the statement in the first sentence of the second paragraph?

2. p. 119 (Fig. 2): The graphical display seems to indicate that more Agent White was sprayed than Agent Orange in Vietnam. Why is that?

3. p. 123: Why would herbicide handlers have the highest mean combat score in view of their job distribution in Table 2, p. 121?

4. p. 123: The first sentence of the Discussion Section is meaningless. This study was not needed to confirm that herbicides were used in Vietnam on a large scale.

5. p. 124: The authors do not provide the basis for the statement given in the last sentence of the first full paragraph. Where are the data that support this statement?

6. p.124: The discussion of the representativeness of the study group misses the point entirely. No amount of internal analyses of respondents will permit an assessment of whether the group is representative of all Vietnam veterans. The authors never compare the demographic & socioeconomic characteristics of their sample with any other external population to judge representativeness.

7. p. 126 (top): Just because 1 percent of the study group said they joined the American Legion because they needed assistance on a special "problem" does not eliminate "membership selection" as a possible source of bias. These data seem irrelevant to an assessment of bias.

8. p. 126 (middle): Their data do not demonstrate "that sufficient numbers of troops are available and identifiable for epidemiologic study of herbicide effects". This statement is a "leap of faith" from very limited and questionable exposure data. From Fig. 3 on p. 120 it would appear (assuming their herbicide exposure index is measuring exposure) that there might be insufficient numbers of men with high exposure scores.

9. p. 127: In the last paragraph of the article the authors claim that the accuracy and precision of their exposure assessment

method "are comparable to, or exceed, those used in many environmental and occupational studies" without giving any basis for this conclusion.

10. p. 148: The authors say that the "internal consistency of the findings also lends credibility to the study". However, nowhere do they present data that support what is really meant by internal consistency, i.e. that a particular association is present in various subgroups of the total study group. By internal consistency, the authors seem to mean that there was a large number of positive exposure-response associations for combat and herbicides. Of course, this is circular reasoning, using the health outcome results to justify the validity of the exposure measures.

11. p. 156 (Table 1): These findings are consistent with the results of the VES telephone interview component. Results for the infrequent conditions should have been tabulated for descriptive purposes and for completeness. Also, all conditions should be shown, not just those that were reported more frequently in the SEA group.

12. p 158 (Table 2 & 3): There is no discussion of why the herbicide handler group does not show an excess of adult acne (OR=0.99) whereas the High herbicide exposure group does show an excess for this condition (OR=1.45).

13. p. 158 (bottom): There is no discussion of the curious finding that benign fatty tumors is the only condition that is positively associated with both combat and herbicide exposure.

14. p. 162 (Table 6): The authors should have pointed out that the correlations obtained, while statistically significant, are <u>weak</u>.

15. p. 163 (Table 8): Same comment as in #14 above.

Pierre Decoufle

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date DEC 21 1988

From Director, NCHS

Subject Review of American Legion Study of CEHIC

To Dr. Vernon Houk
Director, CEHIC

I understand that on December 6 you asked NCHS to review the American Legion-Columbia University Vietnam Veterans Study for study design, sampling, response rates, and analytic methods that the authors used to cope with flaws. The following are some issues raised by the information sent for us to review. We only reviewed the findings regarding "Health and Reproductive Outcomes."

The American Legion study was a retrospective study of a well-publicized suspected toxic exposure experienced by men one to two decades ago. That is, the potential participants of the study were not "blinded" to the hypotheses. As such, there are many aspects that make it difficult to ever do such a study and get reliable, meaningful results. The investigators provided the reader with minimal information relevant to these issues and did not give adequate discussion regarding the interpretation of the findings.

Subject recruitment

The subjects were recruited from the American Legion rolls in six States. There was an attempt to determine all veterans on these rolls that were in the services during the Vietnam era. The number was not explicitly stated, but it appears to be 12,588 (Report #1, p. 3). There was a 54 percent response rate to a mailed questionnaire. However, the investigators provided no information regarding the nonresponders. Hence, it was not stated whether there was a different response rate among veterans who served in Southeast Asia or who suspected that they had been sprayed with Agent Orange as compared to other veterans.

Questionnaire

Many variables requested time in month and year. Given that the period of recall was as long as 20 years, the data from these questions were probably unreliable. Hence, the careful analyses that combined this information with the records of herbicide spraying were also likely to be unreliable.

The questions regarding skin conditions were stated in terms of "ever experienced" these conditions. The article implies, however, that the conditions were current.

Analyses

The criteria for "high," "medium," and "low" exposure classifications were not given. However, from the frequency distribution (EHR, p. 120) and numbers in the tables (EHR, 158-159) it appears that "high" included anyone with an exposure level at or above the mean, i.e. 0.36 - 1.60. That means that, with the unreliability of the question responses, there was probably little difference between the "medium" (.10 - .36) and "low" (0.0 - .10) groups.

Combat and herbicide exposure were confounded. There were inconsistencies regarding the number of veterans in various combat classifications. On EHR p. 119 it was stated that 2087 Southeast Asia veterans had combat scores. However, on EHR p. 160 the total number of Southeast Asia veterans with combat scores was 2845...a number which apparently did not include herbicide handlers. This is unlikely since the total number of Southeast Asia veterans who were not herbicide handlers was only 2858-102 = 2756!

Selected findings regarding "health and reproductive outcomes"

Because the combat and herbicide exposures were confounded, it is hard to determine a primary cause (combat vs herbicide exposure) even if one regression coefficient may appear to be larger than another. Because of the resulting multicollinearity, the standard errors on the coefficients (not given) would be quite large. Although the resulting coefficients may be significantly different from zero, they are unlikely to be significantly different from each other. Therefore, their relative "importance" would be difficult to assess. Further, because of the instability of these estimates, these kinds of regressions often change radically when more subjects are added to the analyses.

The finding regarding the percentage of spouses' pregnancies that resulted in miscarriages is suspect. The miscarriage rate of pregnancies to women in the general population is 20-25 percent. However, this study only reported 7.6 percent for Vietnam veterans and 5.5 percent for others. Clearly, there was a great deal of underreporting. Both the retrospective nature of the study and the fact that most of the reports may have been be proxy reports would have affected the underreporting. Veterans who have no reason to suspect reproductive problems as a result of their previous military experience are likely to forget more miscarriages of their wives than the Vietnam veterans. Therefore, these data provide no evidence that the miscarriage rates have been different for wives of these study subjects.

The health symptom complex is based on symptoms severe enough for the veteran to seek medical attention one or more years following discharge. This means that veterans who may have sought attention while in the military as long as several years after serving in Vietnam would not be included. On the other hand, because of the recent, heavy publicity regarding Agent Orange exposure and these symptoms, veterans of Southeast Asia would have been more likely to seek medical attention regarding these health symptoms. Therefore, with regard to these symptoms, there may have been bias in terms of which group of men would have actually sought medical attention.

Summary

There are several aspects of retrospective studies in general, and this study in particular, that make the interpretation of these results difficult. None of the above findings, and others, were discussed in light of the likely recall bias of this study population. Some of the numbers of subjects included in analyses are inconsistent and no information is given regarding the nonresponders. The authors do conduct largely within group comparisons, however, they are not critical of the effect of strong confounding of the variables of most interest.

M Feinleib

Manning Feinleib, M.D., Dr.P.H.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date December 19, 1988

From Epidemiologist, AOP (F-16)

Subject Environmental Research 1988; 47: 109-209

To Stephen B. Thacker, Assistant Director, Science, CEHIC (F-29)

Stellman et al. present results from their studies of American Legion members and the associations between self-reported health and well-being, and selected "exposures." My comments focus of three aspects of the study: subject selection, assessment of exposure, and other.

1. Subject selection:
   Process: The process of identification, selection, and interviewing subjects was complicated. "Captain organizers" recruit "volunteer researchers" who contacted a random sample from rosters of American Legion members to determine time and places of service. Apparently, the first 15 Vietnam-era veterans who served in Southeast Asia and the first 15 Vietnam-era veterans who served in other areas were sent questionnaires.

   Comment: The selection process allows the possibility for selection bias. The basic problem is that ultimate selection for study was partly dependent on a subjective process (being identified as a Vietnam-era veteran by a volunteer, and returning a questionnaire) and that participation was rather low: 52% to 64%. These limitations of the selection process imply that bias could have affected results. To illustrate this possibility, suppose that Vietnam veterans who had been exposed to Agent Orange and who had some medical problem were more vocal about their war experiences. The military service of such men might be better known to these "volunteer researchers" so that such men could have been more likely to be studied. Whether or not this bias actually occurred is difficult to assess, but the partly subjective process that was used, and the low participation make this source of bias possible.

   Tests of statistical significance are probably not appropriate for assessing selection bias, as was done by Stellman et al. on page 125. The inappropriateness of using statistical tests of significance for assessing confounding is well-developed, published, and accepted (Rothman: "Modern Epidemiology; Little, Brown and Co, Boston), and similar concepts probably apply for selection bias in epidemiologic studies.

2. Assessment of exposure
   Procedure: Agent Orange exposure was assessed from information provided on a questionnaire by the veteran and from information on the HERBS tapes (updated). Briefly, each veteran indicated times and places that he had been located during his service in Vietnam; exposure score was developed by weighting reported locations inversely in proportion to time and distance from reported spray locations.

   Comment: The score and its description have several weakness:
   a. The score is based on subjective information and has not been validated. Some of the scores used by CDC, though different in some ways, had similarities and were not meaningfully associated with dioxin levels.

   b. The half-life of 1 year which is used in the score, though documented for dioxin in some "compartments" of the environment is probably too long for other, potentially important environmental compartments such as dioxin on leaves and vegetation. Although Stellman et al. state that the score was insensitive to large changes in the half life, they do not quantify these "large" changes.

   c. A positive score is given, even if the spray was up to 15 km away. Although the upper limit of the distance used is arbitrary, and although longer distances were weighted less, the 15 km distance seems large given that Ranch hand spray paths were only a few hundred meters wide.

d. Analyses: an important limitation, or perhaps omission, is lack of comments concerning calculation of scores for time periods for which no location was reported. If these periods were assigned a zero score, then the analysis should account for the missing days. Otherwise, results could be biased: men who report more illnesses might also have reported locations for more days because of recall bias, and could, thereby have received a higher score. This scenario, if not addressed, could artifactually create the impression of associations between health outcomes and AO exposure.

e. The herbicide score appears to be strongly associated with combat. If combat is subject to misclassification, and combat leads to certain health outcomes, then residual confounding may exist even after adjustment for the combat score.

f. The score is undefined if the reported location corresponds to a recorded spray location.

3. Analyses:
   a. Analyses: the possibility of residual confounding by combat, etc, does not appear to be fully appreciated (see above).

   b. Statistical tests of significance are probably not the best means for assessing bias (see above).

   c. It's not clear which analyses for herbicide effects were adjusted for combat (even apart from the previously noted limitations of this adjustment; see above) and other covariates.

   d. It's not clear why estimates for combat and skin conditions such as adult acne weren't presented. Were these outcomes associated with combat too?

   e. Control for and presentation of estimates adjusted simultaneously for several potential confounders such as branch of service, military occupation specialty, race, SES, age, and residence would have been useful.

Dana Flanders

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date · December 16, 1988

From Senior Statistician, AIDS Program

Subject Comments on the manuscripts by Stellman, Stellman, et al. on health of Vietnam veterans published in Environmental Research, December 1988

To Stephen M. Thacker, M.D.
Assistant Director for Science
Center for Environmental Health and Injury Control

I read carefully the first paper and the Stellmans' previous paper on estimating exposure. I was particularly interested in this part of this material because I had responsibility for overall coordination of the CDC Agent Orange Validation Study (AOVS), did a substantial part of the work on estimating herbicide exposure for the veterans in that study, and had the main role in writing the report and manuscript describing the AOVS results.

COMMENTS ON ESTIMATING EXPOSURE

Many studies of tissue TCDD levels have shown that Vietnam veterans whose main job was not handling herbicides have levels similar to unexposed civilians of the same age. In addition, the AOVS showed that there is no relation between current TCDD levels and relative opportunity for exposure according to a wide variety of scores derived from the military records or from self-reported exposure. Thus, there is no evidence that typical troops who served in South Vietnam had meaningful exposure to TCDD.

Analyses of herbicide spray and military unit location records show that units were seldom within 2 km of a Ranch Hand spray within a week after the spray (unpublished analysis done for the AOVS). Thus the greatest potential for exposure to herbicides shortly after spraying was likely to result from sprays around base camps. The Agent Orange Advisory Committee recognized that the records are seriously incomplete for these sprays (General Murray report).

As Lilienfeld recently stated, "It is the assessment of exposure that is the cornerstone of any environmental epidemiologic study" (D.E. Lilienfeld, Changing research methods in environmental epidemiology, Statistical Science 1988, 3: 275-280). Thus the validity of the findings in this series of papers depends on the accuracy with which exposure was assessed in this study. I reviewed carefully the original paper describing the exposure estimation procedure (SD Stellman & JM Stellman, Estimation of exposure to Agent Orange and other defoliants among American troops in Vietnam: a methodological approach, Amer J Industrial Med 1986, 9: 305-321) as well as the summary of exposure estimates for the men in this study. Especially in light of the findings in other publications, the authors of these studies must show that they have overcome the recognized difficulties and obtained valid exposure measures. I believe that their measures may be unreliable for the following reasons:

1. The authors' estimates are based completely on Vietnam veterans' recollection of their locations and dates of service, without any apparent validation from military records.

2. The authors' procedure greatly overestimates the relative exposure of veterans who were more than 1-2 km from known herbicide sprays.

3. The authors' procedure implicitly assumes that the only exposure of concern was from contaminated soil and perhaps water, which may result in a substantial overestimate of exposure for those who actually were within 2 km of a documented spray.

The following are detailed comments on these issues.

1. Both published manuscripts report that exposure was estimated by asking veterans the dates they had served at about 100 locations in South Vietnam. The authors appear to believe that the provision of sufficient data to calculate an exposure measure is evidence that the data are reliable (1986, 311-315; 1988, 116 and 119-120). Because of the long half-life the authors used, their exposure measures probably do not depend very much on accurate date information. However, it would seem essential to verify veterans' recollection of where they served by validating a sample of questionnaires with military records. Such records were used in the Agent Orange Validation Study (AOVS); they are the dates during which a veteran served in various units (from his military record), and the locations of those units on those dates (abstracted from military records by the ESG).

2. The exposure measure allows for substantial exposure up to 15 km from a spray (1988, p. 116), with exposure decreasing as the inverse of the distance from the spray. Simulated Ranch Hand sprays at Eglin AFB, Florida, showed exposure decreasing far more rapidly (as a negative exponential), with negligible exposure more than 1-2 km from the center of the spray path (the AOVS report contains a reference to the U.S. Air Force study containing these data). It seems reasonable to believe that most perimeter sprays had no more dispersion than did Ranch Hand sprays, since most of the perimeter sprays would have been from ground level or low altitude. In contrast to this new report, the AOVS used only locations within 2 km of a spray to estimate exposure, a procedure that is in much better agreement with the available data.

In addition, some base camps in South Vietnam were quite large, so that perimeter spraying would not necessarily result in significant exposure for all veterans stationed at that camp. While no details are given, it is possible that each base camp is represented as a point in computing potential exposure in this report. In their 1986 report, the authors show that, for 6 base camps, there are far more herbicide spray "hits" 5-15 km from these base camps than within 5 km (1986, p. 311, Table II). Note also that use only of sprays within 5 km changes the ranking of these base camps with respect to their relative opportunity for exposure.

These considerations suggest that the authors may have substantially overestimated herbicide exposure for many veterans, in contrast to their statement (1986, p. 317) that "Computed exposures will thus tend to underestimate true exposures", and that the exposure scores do not rank relative opportunity for exposure correctly.

3. The exposure measure used here assumes a half-life of 1 year for the decay of TCDD in the environment (1988, p. 116). This is roughly consistent with the experimental data on the half-life of TCDD adsorbed to soil and similar to the half-life of 3 years used to compute the "slow" or E_3 score in the AOVS. However, this half-life is about two orders of magnitude longer than the estimated half-life of several days for TCDD on vegetation. The Stellman exposure measure, therefore, assumes that the significant source of exposure is soil and gives an estimated exposure far greater than that which would be obtained if the important source was TCDD on vegetation. In fact, the relative importance of vegetation vs. soil is unknown.

OTHER COMMENTS

These reports do not seem to contain much of the basic information necessary to evaluate the results of an epidemiologic study, including:

Why were the 6 particular states chosen?
What were veterans told about the purpose of the study?
What were the response rates in Vietnam vs. non-Vietnam vets?
During what dates was the study conducted?
What power calculations were done leading to the choice of the sample size; what was the achieved power for various prevalences? (The only statement about power I found is in paper 1, p. 115, last sentence before "Characterization of Herbicide Exposure") Is power for herbicide exposure better than the Air Force Ranch Hand Study, where we have clearly exposed and unexposed groups?

The dates the study was conducted and what vets were told do matter. Contrary to the statement in paper 1, p. 123, para. 2 of Discussion, vets could have given responses leading to higher exposure scores. A book of maps showing locations of known herbicide sprays was published in California (I don't know date of publication). Thus it could matter whether questionnaires were completed before these maps published.

Representativeness and bias

Are Legion members representative of all vets? Are members in these 6 states representative of Legion members? Are those responding representative of Legion members in those states? There is reason to doubt representativeness:

a. In the AOVS, interviewed veterans who believed they had health problems or were exposed to herbicides were clearly more likely to go to Lovelace Medical Foundation for the medical exam than those who believed they were in good health or had little exposure to herbicides (see Table 2 in the JAMA article). It is plausible that the same bias would occur in those willing to spend time filling out a long questionnaire.

b. There is some possibility that bias could be introduced by the use of volunteers to determine service location and establish contact. These volunteers might have worked harder to get a Vietnam vet with perceived or actual health problems to participate than a similar vet in good health. There was concern about this type of recruitment bias in the original American Cancer Society study of smoking & health (possible reference: TD Sterling, A critical reassessment of the evidence bearing on smoking as the cause of lung cancer. Amer J Pub Health 1975, 65: 939-953).

The relatively low participation rate gives ample room for bias and a non-representative sample. There is very little analysis of potential bias, and I did not find the analysis of representativeness convincing.

John M. Karon

John M. Karon, Ph.D.

December 26, 1988

To: Tony Fowler
From: Robin Morris, Ph.D.
Re: Comments on Environmental Research articles on American Legion Study

Report #1, May 29, 1985:

I am surprised that the hypotheses (pgs. 1 & 2) are stated in such a way. These are not "null" hypotheses and clearly set a psychological set for all participants in the study. I am particularly concerned with the use of Legion "research volunteers" making contact and discussing the study with potential participants. Even if the participants read the original hypotheses, this would bias their views of the study, and effect their responses since participants are prone to support the researchers hypotheses if they know them (I think this is called the Rosenthal Effect in psychology, but can remember for sure, there has been lots of research on this problem). Even though they state that they "volunteers" were trained "in the proper manner of contacting members" (pg. 4), there is no reported methodology to monitor them to ensure it. Given the nature and multiple purposes of the study, I consider this a real limitation before any questions are even asked.

The general classificatory data they have is also of concern. They classify persons as "In-Country" or not. There is no discrimination on how long they were "In-Country", and no controls for this factor in any of the analyses in this report. A related problem is their use of birth year for analyses, not year of service in Vietnam. As we know from VES, the age of the vet at time of service, and the actual year in which that service occurred was an important factor in all of our analyses. They confound both of these issues in their design.

Their combat exposure scale is very similar to the one use in VES. Their summing of scores, and breakdown into low, moderate, or high combat exposure is also reasonable given the nature of the scale and its use in the past. It is still important to note that this is a self-report scale regarding combat exposure, and although reliable (pg. 6), there is no validation of its accuracy. The authors continue to report this data as if it is reality, when all other types of factors, including current psychological functioning may affect one's report on it. In other words, there may be correlations between it and other measures of psychological health, but this does not mean that combat exposure <u>caused</u> the psychological health, only that people who rate themselves high on combat exposure also rate themselves high on depression items, <u>and vice versa</u>. There are numerous studies showing that persons who are depressed, etc. have a tendency to answer all (even unrelated) scales in a more negative manner. This point needs to be kept in mind throughout all of the papers, as the authors clearly overstate the meaning of the findings and don't consider other interpretations which may have equal validity. They have no data to make such directional/causative statements. As you remember, we have similar difficulties in some of the VES analysis.

Another issue which I think shows their tendency to go past their data, is in their statements at the end of page 7 which try to argue that they there is no selection bias among those who join the Legion. Unless they

question all those persons who did not join the Legion, and their reasons for not joining can they make the necessary analyses to address such a issue. What would happen if all those veterans who didn't join said that the reason they didn't was because they didn't want to have contact with miltary related organizations, etc... Then the "military personality" may be alive and socializing with like personalities (which all persons are prone to do) in the Legion. Their logic is very odd thoughtout all of the study reports. I will not detail all such occurances, only note my concern and the biases which appear to be involved.

A major analysis concern for all of the data they report is the lack of more sophisticated co-variate analyses. They rarely control for those data which they know are different between groups in analyses which are confounded by such variables. In addition, they have no "entry" data on these vets when they went into the service. As we know from VES, the GT, enlistment status (drafted, etc.), etc. at times accounted for a great deal of the variance among various analysis groups. They seem to have a very limited statistical model to adjust for such possible factors in their analyses. A good example of this issue is the differences between incomes in some of their groups. They do not control for the vets time since discharge, age, marital status (previous divorces?), employment history, etc. Given the big effects of each of these on income, their results are just not very telling from my viewpoint.

I know that the part dealing with the VA is not of specific relevance, but the lack of control for those men who have used the VA ever, in the recent past, etc., is a major problem with their analysis, again there appears to be a very simplistic analysis model which appears to be focused on presenting a specific viewpoint.

Comments on "Social & Behavioral Consequences" paper (pp. 129-149).

The general items that were used to assess social and behavioral outcomes (pg. 132-133, and actual questionnaire was reviewed) are very limited. Generally, they represent symptom ratings. Only a few are time linked (within the last 6 months). Although some of these probably would correlate with more standardized and valid psychological instruments, one would expect that their validity would be more limited than the standardized tests due to the limited number of items (even though they have reasonable reliability). Of specific importance in all of these data is the paragraph on pg. 139 (1st under psychological well-being section). The fact that all of the variables are highly intercorrelated suggests that these different scales are not really measuring different factors, but probably are measuring general "psychological distress", or something like that. This has been a problem for the scale that much of this has been taken from (PERI). It should also be noted that these measures <u>do not</u> provide a DSM-III diagnosis, no matter what the authors imply. Given that the symptoms are never time-linked, a subject could have had one symptom this year, another last year, and another 5 years ago and ended up with a high score. Their interpretation of some of the findings (pg. 140, 1st pp) still leave alot to be desired. As example, they state that "The correlation is comparatively strong with combat exposure" - compared to what I have to ask, given one is r.=.18, the other r=.30, accounting for less than 2% and 9% of the predicted variance! These are not correlations that I would be excited about, and many psychological journals wouldn't necessarily let you publish such a statement about them. Notice that in

Table 5 (pg. 141), there is not a correlation over the .30, most are under .22, with combat exposure, and the agent orange index correlations are even lower. The mean differences between groups in Table 6 (pg. 141) are also of limited clinical meaningfulness, although clearly statistically significant given the large sample sizes. I feel that such data is misleading suggesting that the Vietnam vets are more psychologically distressed than the non-Vietnam vets, these score differences are minimal (1 point generally out of 20 possible). I also don't understand how the graphs on page 142 (Fig. 6) can possibly represent their data, given that the correlations are all less than .30 between these data. I think this is graphic "manipulation" of the actual relationships between this data. Do those look like such low correlations to you?

I also have great trouble in that they never look at the relationship between drinking, smoking, etc. and any of the psychological data. We all know that these interact with each other, but they do not use them for any comparisons. Again, they come to the conclusion that the psychological problems are caused by Vietnam, as are the drinking problems, etc., when we know that the psychological and drinking problems are highly interrelated, and may account for more of the current findings than anything else.

Comments on PTSD paper (pp. 165-192):

Again, the main issue here is how they diagnosed PTSD. First, their multiple approach to combat exposure classification is a major factor for their findings. Their basic assumption is that any subject who had a high combat exposure score had to have had exposure to a traumatic event, as required by the PTSD criteria. This is not always accurate, as people working on transportation details may have seen lots of dead bodies, but never have been in life-threatening situations, or traumatized. Anyway, as can be seen by their data, PTSD rates all depend on how you cut the combat exposure index, which of course is correlated with PTSD symptoms, etc. Again, there is some circularity to this approach to this disorder's definition. Their approach is again generally using a symptom checklist without time frame (-since your d/c from service!). No DSM-III diagnosis is made without a timeframe for symptom co-occurrence, as has been discussed before. In addition, they diagnosis no other disorders whose symptoms may be similar, if not identical (anxiety disorders, depression, substance abuse, etc.). Therefore, there is no way to identify just those vets who had PTSD, when they had it, or what else they may have also had. They also don't address other traumatic events in their lives (1% maybe had them), nor what "often" etc. may have meant to a particular vet. I do not consider this approach to provide a DSM-III PTSD diagnosis. The best is does is provide a group of symptom ratings (pg. 182) over a number of years (different for different vets of course). Yes there may be something in the data of interest, but I don't see how you can get it.

On page 183, they take the mean values of these PTSD symptoms.. This is not very meaningful when you figure that one vet may score 4-5 points on 5 symptoms over a 15 year period and get a score of 20, while another vet may score rarely (2 points) on 10 symptoms over the past month and also get a score of 20. Are these men the same? I would be more concerned with the second rather than the 1st in some instances. They treat them in their analyses as identical.

Page 4, Review Am. Legion Study

As you can see, I'm not highly impressed with the psychological methodology, the analysis sophistication, nor the interpretation of the data presented. After the VES, all of these issues are too important and if you don't collect good data, there is just not much you can say about the findings.

If there are any questions for me, I'll be back to Atlanta on Jan. 2 (afternoon).

December 20, 1988

Medical Epidemiologist, Behavioral Epidemiology and Evaluation Branch,
Division of Chronic Disease Control and Community Intervention, CCDPHP

Comments on the Study by Stellman et al.

Stephen B. Thacker, M.D.
Assistant Director for Science, CEHIC

General Comments:

This is a cross-sectional study based on self-reported information. The results are very similar to the interview results from VES (Vietnam Experience Study) - almost all outcomes are reported more often by Vietnam veterans than by other veterans, and, among Vietnam veterans, those who report handling herbicides or more combat experience reported higher rates of most outcomes. As with VES, it is possible that these higher self-reported frequencies are, in part, due to recall bias. One difference between this study and VES is the use of a herbicide exposure index based on the MERBS tapes and the veteran's report of his specific locations of service in Vietnam. This index also predicts self-reported outcomes among Vietnam veterans.

To evaluate the Stellman herbicide exposure index, we could ask Agent Orange Validation Study participants to complete the Stellman Vietnam location instrument. We could then compute exposure scores per Stellman and compare these scores to previously measured serum dioxin levels. We could similarly compute these scores for VES examination participants and see whether there is an association between this index and certain objective measures which correspond to the self-reported findings from the Stellman study (i.e. - "fatty skin tumors", evidence of acne, etc.).

Specific Comments

Methods:

1) The study population is not representative of the total Vietnam-era veteran population as it includes only American Legion members and is 98.5% white. This unrepresentativeness restricts generalization of the results.

2) Because they did not restrict their population to men who served a single term of enlistment and because most career servicemen during the Vietnam-era served at least one term in Vietnam, the Vietnam group is likely to include a higher percentage of career servicemen than the comparison group. This limits comparability between the groups.

3) The method of recruitment allows self-selection of study participants.

4) The overall response rate was low (53 - 64%), increasing the possibility of selection bias. Neither the exact overall response rate nor the response by POE is specified. They attempt to address non-response by comparing responses from a 'high' response state (Minnesota) and a low response state (Pennsylvania), but this is not helpful as it fails to address differences between non-respondents and respondents. Besides, the response was poor from all six states (64% or less).

5) They have no objective measure of dioxin exposure with which to validate their exposure index. Furthermore, I question the ability of a person to recall exact time and place of service in Vietnam 20 years after the fact.

6) Their five symptom scales are statistically derived rather than clinically based. It is unclear whether they are biologically plausible.

Results:

1) The results are nonspecific as the odds ratio is increased for almost all outcomes.

2) Our troops in Vietnam experienced higher incidence rates of venereal diseases and viral hepatitis than troops who served elsewhere during that era (see Ognibene AJ, Barrett O Jr, eds. General medicine and infectious diseases (vol II): Internal medicine in Vietnam. Washington D.C.: United States Army, Office of the Surgeon General and Center of Military History, 1982:233-256 and 419-442). The higher rates of these conditions reported by Vietnam veterans in this study probably reflect events which occurred while the veteran was still in the service.

Thomas R. O'Brien, M.D., M.P.H.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date · December 20, 1988

From Chief, Epidemiologic Studies Section, ERSSB, DCDCCI, Center for Chronic Disease Control and Health Promotion, (F11)

Subject Comments regarding the Vietnam Experience Studies of Stellman et al.

To Stephen B. Thacker, M.D., M.Sc., Assistant Director for Science, CEHIC, (F29)

Most of my comments have to do with sample selection, response rates, questionnaire construction, and creation of combat and herbicide indices, as potential biases introduced by these components make interpretation of results difficult.

American Legion Members as the Sampling Frame. This study, funded by the American Legion, was limited to members of this organization. The authors admit that they do not have a 'representative' sample of Vietnam Era veterans, since American Legion members represent the 'solid middle section of white America'. Demographic data on the both the total sample and respondents is sketchy, but the authors did indicate that 98% of the participants are white. The authors also indicate that participants have been resocialized sufficiently to join the American Legion. The majority view it as a social organization, but information on services available to veterans is also provided. The authors suggest that a study based on this group represents a 'best case' analysis of the potential health and social effects of the War. It is also possible, given some of the issues discussed below, that the biases introduced by the sample selection and information collection procedures could lead to an over-representation of veterans with residual problems that they attribute to Vietnam service.

Sample Selection. The authors chose a cross-sectional sample from American Legion membership roles from six states (CO, OH, MD, PA, IN, and MN) on a specific date. After exclusion of those with 20 or more years of membership, one-seventh of the records were selected at random. Those in the one-seventh sample were sent a postcard to indicate if he was a Vietnam Era veteran, since this information is not included in Legion membership records. Those who did not return the card (an unspecified proportion) were contacted by the Post Adjutant to identify those known to be non-Era veterans. Vietnam Era veterans and those of unknown status were then contacted by 'volunteer researchers' to determine actual service location, and to encourage participation. The authors appear to have adopted this strategy from the American Cancer Society (ACS) where they were once employed. Recruitment of volunteers for assistance may have its place in studies without a strong a priori hypothesis known to the volunteers, but in this case, the hypothesis is quite clear to the volunteer researchers, to the American Legion, and to the participants.

Vietnam veterans with health or psychological problems and non-Vietnam veterans without problems could have selected themselves for the study by returning the postcards. Even more disturbing, the volunteer researchers could have selectively influenced participation. The researchers were given 'goals' to identify 15 Southeast Asia and 15 non-Southeast Asia veterans for the study. With these expectations, it is easy to presume that a well-meaning volunteer could have chosen the 'worst' Vietnam and/or the 'best' non-Vietnam veterans. These unorthodox recruitment procedures are not used in large-scale epidemiologic studies except by the ACS, yet the authors do not explain why they used them or why they would not introduce bias in a study of this type. At least some of the service-related information provided by participants could have been verified by obtaining discharge records. Information on at least some veterans, such as place of service, service dates, rank, and discharge status could have been verified from discharge records, yet the authors did not do so. The the extent of the potential bias introduced by this sampling scheme cannot be evaluated, because the authors do not provide baseline demographic information on the original sample and the selected population. Even basic information, such as distributions by type of service (Army, Navy, etc.) is not provided.

Questionnaire Construction. The questionnaire is designed so that information on combat, herbicide exposure, symptoms of post-traumatic stress disorder (PTSD), social factors upon return, and helpfullness of the Veterans Administration are collected before the outcome data. Also, the tone of the questions implies that the veterans did have problems upon return. The herbicide section even includes questions on acute symptoms following exposure, thereby reinforcing its potentially harmful effects. Placing the exposure questions before the outcome questions is not standard practise, and the potential for biasing subsequent responses is clear.

Data Collection. Information was obtained by mailed questionnaire. It appears that the authors sent 12500 questionnaires and received 6810 (54.5%), a low response rate for survey research. With mailed questionnaires, one can never be assurred that the intended person has completed the questionnaire or that he has not received undo assistance. With 'volunteer researchers' available, the ability to receive this sort of help is enhanced. The authors suggest their sample is not biased because reported herbicide and combat levels by posts with high response rates compared to those with low response rates, although their outcome data suggest otherwise. Nearly 9% more men from high response posts report excellent health than those from low response posts. This suggests that those with the most health or psychological problems could have been recruited first, with low response posts never getting around to recruiting other veterans. It might be difficult for volunteers to selectively recruit veterans by exposure because the scaling procedures are not known, but it would be very easily to conciously or subconciously

select veterans who seem to be in poor health. The usual information on methods, such as the number of mailings conducted and demographic characteristics of responders was not provided. In the VES, we found only one factor that differentially influenced participation rates in the examination component between Vietnam and non-Vietnam veterans. Non-Vietnam veterans with higher education levels were more likely to participate in the examination, presumably because they understood the importance of their participation. With their low response rates, it is quite possible that socio-demographic differences attributed to Vietnam service may be heavily influenced by differential motivational factors for participation.

Herbicide Index. Drew Baughman, John Karon and others are more familiar than I with construction of herbicide indices, but a few points come to mind. Only 72% of Vietnam veterans provided sufficient information on location for estimating herbicide exposure. For exposure data, it is not clear why a one-year half-life was chosen, and based on our knowledge, this seems quite long. The authors indicated they counted all sprayings which ever occurred near each location reported by the veteran. From their report, it does not appear that they excluded sprayings that occurred after the veteran had been in the location of interest. For location data, veterans were asked to give dates of service for about 100 locations of major troop activity. It would be difficult to remember specific dates and places nearly 20 years after the fact. The questionnaire listed the names of base camps, villages, etc. (along with a somewhat illegible map of Vietnam), yet most herbicide exposure would have occurred in more remote areas. Veterans would think they were most heavily exposed when walking through defoliated areas, although by that time, the chemical constituents of the herbicide would have decomposed. In contrast, veterans would have been most exposed shortly after spraying and before chemical decomposition when the jungle looked relatively normal. It would not be unusual for veterans to perferentially remember time spent in defoliated areas, and with the one-year half-life built into the model, these men would be considered exposed. For personal exposures, veterans were asked if they had ever handled herbicides. Veterans could have responded positively if they handled many different types of chemicals, which they now presume were herbicides. Most of the chemicals used near base camps, etc. were insecticides, not herbicides. Thus, the index could represent belief in exposure to Agent Orange rather than actual exposure. In good faith, veterans could think they were exposed because they walked through defoliated areas, and because they sprayed or were otherwise exposed to unknown chemicals. The potential for intentional exageration of exposure is also clear. This variable should not be discounted because it does not reflect objective exposure. Our studies suggest that belief in exposure rather than objective exposure as measured by blood dioxin levels, is a strong risk factor for many adverse outcomes, and in particular, depression.

Combat Index. The study includes groups other than ground troops, but focuses only on ground troop experience. For instance, fixed wing pilots or medical personnel could have had traumatic combat-related events, that are not described by this index. The index focuses on frequency not intensity. Seeing a dead man on five separate occasions could get more weight than being involved in one large ambush. The combat index has limitations, even if it is confined to ground troop experience. The questions are redundant and their intent is unclear. For instance, shooting one Vietnamese could elicit a response to 5 of the 8 questions. The scoring procedures are not weighted according to the severity of the experience. For instance finding yourself in a situation you thought you would never survive receives equivalent weight as firing your weapon or seeing dead enemy. None of the combat indices, including the one used in the VES, are ideal but since combat is their major exposure of interest, they could have asked a more extensive battery of questions rather than a screening battery.

Psychological Scales. Most scales chosen represent general adjustment and not specific psychiatric diagnoses. The scales are all said to be reliable (e.g. repeatable), but they do not provide documentation of their reliablility or any discussion of their validity.

Analytic Strategy. Crude associations are reported in most instances. Joint effects of combat and herbicide exposure were assessed (and hopefully the 'non-significant' main effect of herbicide exposure was left in the model with and herbicide-combat cross-product term), but collected data on demographic variables or smoking, drinking and drug use were not included in multivariate models.

In summary, this study is difficult to interpret due to major problems in study design and execution. Of these, problems with sampling, with questionnaire design, and with low response rates appear to have the most potential for introducing bias that cannot be corrected or otherwise evaluated. The authors have made interpretation of their findings more difficult by not providing standard tables on demographic distributions for the original sample, the participant sample, or the subsample that provided sufficient information for estimation of herbicide exposure. Some of the provided information on service experience could have been cross-checked by reviewing discharge records for at least some veterans. The accompanying editorial implies that evaluating herbicide exposure is not much different than for retrospective studies of exposure to workers where individual exposures are not measured. The analogy is misleading, because for the occupational studies, you know from objective records that the employee was in an area with potential for exposure, and that workers are exposed during operations. In this study, we do not know if veterans were in spray areas at the time of spraying and we do not know if any dose, let alone a measurable dose, was received. Findings from our dioxin study (that were initially surprising to us), should have been addressed in some manner rather than just labeling our conclusions as "nihilistic."

I hope these comments have been useful, and I would be most interested in seeing a copy or your final response.

Nancy Stroup

Nancy Stroup, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Agency for Toxic Substances
and Disease Registry

Memorandum

Date January 5, 1989

From Member, Agent Orange Science Panel

Subject Review of the American Legion Studies published in Environmental Research

To Chairman, Agent Orange Science Panel

I have reviewed the editorial and 4 epidemiological studies regarding Vietnam veteran members of the American Legion published in Environmental Research, Volume 47, Number 2, December 1988. I have, however, restricted my comments to portions of the editorial by M. Gochfeld, the 2 articles by S. Stellman et. al., and 1 article by J. Stellman et. al. which relate to herbicide exposure.

Editorial: New Light on the Health of Vietnam Veterans -

I found this editorial to be unnecessarily inflammatory in a manner better fit for the newspapers than a scientific journal. Expressions like "in the face of remarkably complacent responses by the Department of Defense and the Veterans Administrations" are inappropriate. Gochfeld argues that broad surrogates of herbicide exposures, such as service in Vietnam, are inappropriate predictors of exposure and that blood dioxin levels are the best measures of exposure, but seems to dismiss the work performed by the Centers for Disease Control which did perform blood dioxin tests on a number of ground troop veterans. This testing was not able to adequately define an exposed group of veterans for evaluation. Despite arguing the importance of having a biological determination of exposure, Gochfeld then tends to endorse the exposure index created by Stellman and Stellman which is an unvalidated predictor of exposure.

Although I find the articles interesting in an exploratory or pilot sense, I would not agree with Gochfeld that they represent "a landmark in veteran health research and occupational epidemiology."

Combat and Herbicide Exposures in Vietnam among a Sample of American Legionnaires -

The only conclusion that I can strongly agree with in this paper is that "our analysis demonstrates conclusively that mere presence in Vietnam cannot be used as a proxy for exposure to Agent Orange." This statement is not an original finding, but supports work previously performed by the Centers for Disease Control. This article, and their previous work published in 1986, describe a complicated mathematical index which addresses multiple factors thought to increase the risk of exposure to Agent Orange, such as assignment, occupation, and proximity to spraying.

The authors report that their exposure index to Agent Orange and combat experience were associated. This is not surprising since, I suspect, that the largest number of persons in the jungle where spraying occurred were ground combat troops.

Despite the apparent background work performed by the authors and complexity of the index, no information is provided about their model to make it a better predictor of exposure than others previously created. The Department of Defense, the Veterans Administration, and the Centers for Disease Control used the Department of Defense records to create a predictive model. These government agencies, however, attempted to validate their model with biological testing and found that they could not define an exposed group of Vietnam veterans. The Stellman and Stellman is not validated, and, thus, we do not know if it is predictive of exposure. In some analyses the authors use occupation as evidence of exposure, which may be a more reliable indicator, as was found in the Ranch Hand studies.

Health and Reproductive Outcomes among American Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam -

This paper describes the rate of self reported symptoms and diseases among study participants. The study cohort was defined via mailing and contact with American Legion posts. The actual participation rate for the study group was 42% for those serving in Southeast Asia and 58% for those serving elsewhere. These participation rates are not very high, and the presence, type, and direction of bias generated by the low participation are not predictable. One may be concerned about a potential bias, that participation may have been more likely among persons concerned about the effects of the Vietnam experience or those who believe that their health has been adversely impacted. This, however, cannot be evaluated.

The authors report significant elevations in the reporting of benign fatty tumors, adult acne, skin rash with blisters, and increased sensitivity of eyes to light. This corresponds to the elevated reporting of multiple health conditions among the Vietnam Veterans among the Centers for Disease Control Vietnam Experience Study (JAMA, May 13, 1988-Vol 259, No. 18). In the Centers for Disease Control Study all veterans interviewed and those veterans eventually examined reported multiple health problems, many similar to those found by Stellman et. al., including chloracne and other skin conditions. These conditions, however, were not confirmed upon dermatological examination. One must be concerned that over-reporting may be responsible for the Stellman et. al. findings, but transient adverse health effect that have resolved cannot be discounted. The herbicide handlers did not have large number of significantly elevated adverse health conditions, but did report more skin rash with blisters and change in skin color.

Stellman et. al. also report a significant increase in reported spontaneous abortions among wives of Vietnam veterans. I could not determine if the information about spontaneous abortions was provided by

the veteran or his wife. Previous studies report that men are poor sources of information about their wives maternity/gynecological medical history.

Social and Behavioral Consequences of the Vietnam Experience among American Legionnaires -

This paper only describes herbicide exposure to be interaction terms in the relationship between combat and adverse social and behavioral outcomes.

Conclusions:

I find this series of papers to be interesting as pilot studies and they would be informative if many more definitive studies had not already been performed. Validation of the exposure index would strenghten the results of this data. If the exposure index truly predicts exposure, as defined by dioxin blood testing, we could be more certain that the truly exposed veterans had been studied. Without this information the study of presumed exposed persons for non-validated self-reported health problems should only be considered as exploratory rather than definitive.

Jeffrey A. Lybarger, M.D.

12/18/88

Dr. Vernon Houk, Director
Center for Environmental Health and Injury Control
Centers for Disease Control, Mailstop F-29
1600 Clifton Road
Atlanta, GA 30333

Dear Dr. Houk:

This is in response to your request for my critique of the recently published American Legion studies of Vietnam veterans. Although they drew their sample in a way that is very different from the explicit and random method used in CDC's Vietnam Experience studies, their mailed questionnaire (subjective) findings are very similar to the telephone interview (subjective) findings reported by CDC. Their failure to consider the objective data available to them from CDC and from the New Jersey group, led them, however, to an unbalanced (too narrow) interpretation of their data.

Methods: In their studies they used a self-reported combat scale analgous to the one used by CDC. Their computation of an herbicide exposure opportunity index was based on the same sets of spray data used by CDC, and their OEI formula is analogous to the E2 score used by CDC in its dioxin (TCDD) validation study in III Corps area veterans. The main methodologic difference was that in their questionnaire each veteran was given an annotated Vietnam map, with place names and military unit names, and was asked to recall and record his location by month and year. With time limited to month, they were forced to use the assumption of a rather slow TCDD decay curve in their OEI formula. In its TCDD study CDC used military records to identify the unit and probable location of each veteran for each day, thus allowing the use of both rapid and slow decay models for separate analyses.

Findings: Both sets of studies found that self-reported combat exposure and self-reported or computed herbicide exposure opportunity are correlated, and that combat exposure correlates with subsequent anxiety, depression, post-traumatic stress syndrome, and certain self-destructive behaviors. In other words, we agree that combat tends to leave long-lasting "invisible wounds." Furthermore, both sets of studies found that combat-exposed people (often also believing that they were exposed to herbicides) tend to report more physician visits and more "yes" answers to a wide variety of symptoms and illnesses, including more miscarriages for their wives. Because of its larger budget, CDC was able to seek objective confirmation of some of the subjective data. Upon physical examination and laboratory tests, most of the differences between the Vietnam and non-Vietnam groups disappeared. Further, CDC found low residual TCDD levels (used as a marker of prior herbicide exposure) in the Vietnam veterans, not different from the levels found in the non-Vietnam group. Among the Vietnam veterans, there was no correlation between TCDD levels and either self-reported herbicide exposure or exposure opportunity scores calculated several ways.

High residual TCDD levels are being found by CDC's laboratory, however, in Air Force Ranch Hand veterans exposed occupationally, in civilians who are former herbicide production workers, in people with heavy environmental exposures in Missouri, and in people who were heavily exposed to the fall-out of an explosion in a herbicide factory in Italy. This last group has residual TCDD levels several orders of magnitude higher than the highest level found either in the CDC studies or in Vietnam veterans studied by the New Jersey group, yet chloracne is the only ill-effect seen so far in the Italian group.

Interpretation: The authors of the American Legion studies apparently did not read the studies mentioned above, since they accept their own subjective data at face value, without comment as to alternative explanations for those findings. When one views all of these studies, including those with very costly objective data, there is a clear and consistent alternative set of interpretations which is not at variance with any of the data reported to date by any study group:

1) Many anxious, depressed combat veterans have psychologic and physical symptoms.
2) Many of them also were in and around herbicide applications in Vietnam, and they have subsequently been told about dioxin and its "extreme" toxicity.
3) Many of them, therefore, attribute their current symptoms to past herbicide exposure.
4) Very, very few of them actually absorbed significant quantities of TCDD (and therefore other harmful herbicide constituents) from the types of casual or non-repetitive exposures they experienced.

Therefore, studies of adverse effects produced by herbicide exposure cannot be efficiently done from general samples of Vietnam veterans. This logical conclusion from the available data is not "nihilistic", as implied in the editorial accompanying the American Legion reports. Such studies can be efficiently done in the small number of people with clearly heavy, repetitive (usually occupational) exposure. Such studies are under way. Preliminary reports suggest the hypothesis that TCDD is substantially less toxic to man than it is to guinea pigs.

One is left wondering why the authors of the American Legion studies and the author of the accompanying editorial seem to have selectively ignored recent objective data available to them for arriving at a more balanced interpretation of their subjective data.

With best regards,

Robert H. Wolfe, MD, PhD
Hawaii Department of Health
(formerly Chief Scientist,
Agent Orange Studies, CDC)

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JAN 19 1989

The Honorable G.V. (Sonny) Montgomery
Chairman
House Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515-6375

Dear Mr. Chairman:

As promised in my recent letter, the Science Panel of the Domestic Policy Council Agent Orange Working Group (DPC/AOWG) has reviewed the American Legion Epidemiologic Studies of Vietnam Veterans (Environmental Research 1988; 47109-209). At a specially convened meeting of the DPC/AOWG on January 10, 1989, their evaluation was reviewed and received concurrence.

In sending you the review, I include the letter and summary of findings from the Chair of the Science Panel. Of particular note, we have included the individual opinions of each scientist by name. Missing from the individual opinions is that of the representative from the Congressional Office of Technology Assessment (OTA) who contributed much to our deliberations. OTA will be making its own review and report under separate cover.

In sending this report, I also bid farewell as the Chairman of the DPC/AOWG. The important work of research will continue under new leadership until this vital issue is resolved.

It has been a privilege to have served our Nation's veterans and to have worked with you in the process.

With warm personal regards,

Sincerely,

Don M. Newman
Chairman
Domestic Policy Council
Agent Orange Working Group

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333
(404) 488-4111
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JAN 0 5 1989

MEMORANDUM TO: Members, Science Panel, AOWG

FROM: Chairman, Science Panel, AOWG

SUBJECT: Review of the American Legion/Stellman Papers

Attached are copies of the reviews we have received to date on the subject study. There will be a Science Panel meeting from 11 a.m. to 1 p.m. January 10, 1989, in the Under Secretary's Conference Room, 6th Floor, Hubert Humphrey Building, to discuss this and attempt to prepare a final document for transmission to AOWG. This will be followed at 2 p.m. by a joint meeting of the AOWG and the Science Panel in the same room.

I am personally not involved in this review process but am only the convener of meetings and the sender of papers. Dr. Stephen Thacker, Assistant Director for Science, Center for Environmental Health and Injury Control, is taking the lead in coordinating these responses and preparing the final document.

Sincerely yours,

Vernon N. Houk, M.D.
Assistant Surgeon General
Director
Center for Environmental Health
and Injury Control

Attachments

cc:
Dr. Stephen Thacker

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

(404) 488-4111
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January 9, 1989

MEMORANDUM TO: Mr. Don M. Newman
Chair, Domestic Policy Council, Agent Orange Working Group

FROM: Chair, Science Panel, Agent Orange Working Group

SUBJECT: Review of the American Legion Study Papers Published in Environmental Research, December 19, 1988

Because of concern about my own potential bias, I did not direct or participate in this review The response from the Center for Environmental Health and Injury Control, Centers for Disease Control, were coordinated by Stephen B. Thacker, M.D., M.Sc., Assistant Director for Science, who also chaired the meeting of the Science Panel. My role was limited to convener and movement of paper to the various members of the Science Panel.

The Science Panel did not review the final article in the series entitled "Utilization, Attitudes and Experiences of the Vietnam-Era Veterans with the Veterans Administration Health Facilities: The American Legion Experience,in great detail. However, the Science Panel concurs with the reviews done by Dr. Han K. Kang and Dr. Lawrence B. Hobson of the Veterans Administration, which are attached as a portion of this communication.

Despite several requests, we were never able to obtain the protocol for this study. We did obtain a copy of the questionnaire but from a source other than the American Legion or the authors of the papers.

Included for transmission to the Congress is a summary review of the nine responders from the Center for Environmental Health and Injury Control, CDC, in addition to their individual reviews. Also included are reviews from Dr. Lawrence B. Hobson and Dr. Han K. Kang of the Veterans Administration; Dr. Manning Feinleib, Director, National Center for Health Statistics, CDC; Dr. Marie Sweeney from the National Institute of Occupational Safety and Health, CDC; Dr. Jeff Lybarger of the Agency for Toxic Substances and Disease Registry, Public Health Service; Colonel William H. Wolfe of the Department of the Air Force; Dr. John F. Young of the Natoinal Center for Toxicological Research, Food and Drug Administration; Dr. Donald Barnes of the Environmental

Protection Agency; and Captain David Uddin of the Department of Defense, accompanied by a review prepared by Dr. Jerome Bricker, consultant to the Department of Defense, regarding the article, "Combat and Herbicide Exposure in Vietnam Among a Sample of American Legionnaires" by Stellman, et al, American Journal of Industrial Medicine 9:305-321 (1986), which apparently was the basis for the herbicide exposure cited in the American Legion studies.

The following is the review by the Science Panel.

The data presented in the American Legion report of the Epidemiologic Studies of Vietnam Veterans (Environmental Research 1988; 47:109-209) do not support the conclusions drawn by the authors. The study is seriously flawed due to major problems in study design and execution. First, there is potential selection bias due to non-random sampling and low response rates. Second, there is potential information bias due to poor questionnaire design and the analysis only of self-reported data without external validation. Probably of greatest concern, any observed association between combat or herbicide exposure is confounded by the investigators' use of subjective measures of combat and herbicide exposure. Combat exposure was not validated by comparison with military records. The herbicide exposure index used by the authors has not been validated, and based on the Agent Orange Validation Study and the Ranch Hand Study, does not accurately predict exposure. Because of these problems, the results of the American Legion report are of little or no value in further understanding the Agent Orange issue. The collective decision of the Government not to proceed with the CDC Agent Orange Study was correct and is not affected by the American Legion report.

Interpretion of the findings are made more difficult by the absence of standard tables on demographic distributions for the original sample, the participant sample, or the sample of veterans that provided sufficient information for estimation of herbicide exposure. Some of the information provided on service experience could have been cross-checked by reviewing discharge records for at least some veterans. The American Legion reports as well as the accompanying editorial imply erroneously that evaluating herbicide exposure in this study is not much different than in retrospective studies of exposure to workers where individual exposures are not measured. The analogy is misleading because in well-conducted occupational studies, one knows from objective records that the employee was in an area of potential exposure and that workers are exposed during operations. In contrast, in the American Legion study, we do not know if veterans were within miles of a sprayed area, and we do not know if any dose, let alone a measurable dose, was received.

Discussion of the findings of the American Legion study is incomplete. Findings from the Vietnam Experience Study (VES), the Agent Orange Validation Study, and other important studies should have been addressed more thoroughly. For self-reported health outcomes, the results are similar to those obtained with the VES questionnaire. As with the American Legion study, almost all outcomes in the VES were reported more often by Vietnam veterans than by other Vietnam-era veterans. Those Vietnam veterans who reported either handling herbicides or having more combat experience also reported higher rates of most outcomes. Most of the verifiable self-reported

conditions, however, were not substantiated by objective evidence obtained during the physical examination. It is not clear why the authors of the American Legion papers, as well as the author of the accompanying editorial, ignore these available data which would have helped them interpret their subjective data.

When one views the full range of the studies on Vietnam veterans, including those with detailed objective data, clear and consistent conclusions emerge:

1) Many Vietnam veterans report psychologic and physical symptoms. Psychological abnormalities have been demonstrated by objective evidence to be slightly more prevalent in Vietnam Veterans. Combat-related Post Traumatic Stress Disorder has been shown to be a problem in several studies. Almost all physical abnormalities have not been confirmed.

2) Many Vietnam veterans also were in and around herbicide or pesticide applications in Vietnam, and they have subsequently been told about dioxin and its "extreme" toxicity.

3) Many Vietnam veterans, therefore, attribute their current symptoms to past herbicide exposure.

4) Very few Vietnam veterans, unless occupationally exposed (e.g., sprayer or mixer), have been shown to absorb significant quantities of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (and therefore other harmful herbicide constituents).

Because of the selected and limited exposure of soldiers in Vietnam, studies of adverse effects produced by herbicide exposure cannot be efficiently done from general samples of Vietnam veterans. Studies which can provide more precise measures of the effect on humans of TCDD are in progress in the small number of people with serum levels of TCDD's markedly above background due to heavy and repetitive (usually occupational) exposure. The major studies are the Air Force Ranch Hand Study, the NIOSH Mortality and Morbidity studies, and the studies around the Seveso incident in Italy. Because of the documented absence of exposure in ground troops in Vietnam, even if these ongoing studies find exposure-related health effects, they cannot be applied directly to the vast majority of Vietnam veterans.

Vernon N. Houk, M.D.
Assistant Surgeon General
Director
Center for Environmental Health
and Injury Control

DEPARTMENT OF THE AIR FORCE
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235-5301

30 DEC 1988

Vernon N. Houk, M.D.
Director, Center for Environmental
Health and Injury Control (F29)
Centers for Disease Control
1600 Clifton Road, NE
Atlanta GA 30333

Dear Dr Houk

My comments concerning the series of reports on the American Legion/Columbia University study of Vietnam veterans fall into five primary areas: the exposure index, statistical interpretation, questionnaire format, bias, and literature review. Many of my comments cross several of these areas. I have summarized my impressions below but have included specific comments about each individual report or document in an attachment.

The most significant problem of these reports is the calculation of exposure indices based on probabilistic models. The exposure indices used by these authors is similar in many respects to the index used in the CDC validation study. The CDC index was the more accurate of the two since it was based on records of actual troop locations rather than memory of respondents nearly two decades later. Even the more accurate CDC index was found to be invalid as a measure of herbicide exposure. Locations of military service were provided from memory by the respondents and the authors made no attempt to determine the accuracy of those reports. They state that "lying" by respondents would not affect the index, but otherwise ignored the misclassification that could have resulted. These data were collected only to the general area of named towns, villages, and military areas by month. In contrast, the HERBS tapes contain data by day and time. This difference in precision further limits the comparability of these data sources.

The initial article on the exposure indices was published in 1986, before the CDC validation data were available. However, the authors had ample time before the publication of the reports in Environmental Research to take those results into account. They did not make use of the CDC work despite more than 12 months in which to make revisions.

The authors also make several untenable assumptions in calculating the indices. They use an estimate of 1 year as the half-life of dioxin in the environment; however, the half-life is on the order of hours to days as long as the dioxin is not bound in the soil. Once in the soil, its availability to troops traveling through the area would be minimal. The use of up to 15 km. from herbicide spraying is also an overestimation of the area of spray drift. In the light of the imprecision of determining locations of service, an area this large was probably necessary in order to have enough "exposed" men to

study. Terrain features and prevailing winds are also ignored in the index. Troops upwind of spraying and those protected by high terrain would not have been exposed.

The use of sophisticated mathematical techniques to calculate the indices does not automatically make them valid. The indices are only as good as the quality of the primary data, which is known to be invalid. The fact that the authors cite a high correlation between two of their indices (r=0.88) does not make either index accurate or valid. It is likely that only the 83 men who reported handling herbicides were actually exposed. This group represents only approximately 4% of the studied group.

The questionnaire is poorly designed. The data on illicit drug use are likely to be seriously underreported. Data of this type must be collected by random response techniques to obtain reasonably accurate data. The location of the questions about attitudes toward the VA before questions on health could have biased subsequent responses. The answer choices are unbalanced with three "true" choices and only one "false" choice. Many of the questions are also biased in wording; the use of words like "fully" and "all" should not be used. Veterans not needing pension or compensation services should not be expected to be "very" knowledgeable about these programs. Many questions ask for opinion about "most" veterans; this is biased. Questions are generally superficial and choices are often poor, leading to possible sources of bias. Questions about attitudes toward the VA are generally biased in wording. Some endpoints such as "skin rash with blisters" are unnecessarily vague, making interpretation hard, while the authors ignore the fact that all endpoints were "reported"; none were verified.

The interpretation of correlation coefficients throughout the reports is flawed (0.08 and 0.15 are NOT significant correlations). Most correlations between the exposure index and endpoints are .30 or less, a level that shows poor correlation at best. The fact that correlations were all statistically significant is irrelevant. The low p value is an artifact of large sample size and the sum of all pairwise relationships in the correlation matrix. This p value has no bearing on the validity of the correlations, with most showing only poor associations at best. The p values only indicate a measure of pairwise variance of large sample sizes and not the validity of the correlations.

All of the conclusions may be biased by the characteristics of Legion members. Use of American Legion members could induce significant selection bias, due to differences between members and nonmembers. The use of "volunteer" researchers may also generate bias in identification. There is no method of quality assurance of their work. The use of Legionnaires raises the issue of significant selection bias since they are not representative of all Vietnam veterans. The authors demonstrate lack of participation bias between SEA and non-SEA vets but not between members and nonmembers. Do Vietnam vets join the Legion in different patterns than non-Vietnam vets? This issue is not addressed and could cause severe bias. The racial distribution is markedly different. Blacks are underrepresented in the study (only 1.5%). These

results could be biased by the patterns of membership in the Legion. This finding may represent reporting bias, but the possibility is never considered by the authors.

The statement that "Mean levels of Agent Orange exposure were ALWAYS significantly higher in . . . miscarriage . . ." appears unlikely. Surely some miscarriages occurred in women married to "low" men. This elevation in every case is highly to highlight the effect of overreporting. The use of Legion representatives who work full-time in monitoring the VA to develop the questions is inappropriate.

The editorial group appears to be quite limited with 22% currently at Mt. Sinai (13 of 58). This fact, coupled with the failure of reviewers to recognize the results of the CDC validation work, leads me to doubt the thoroughness of peer review. The subjective opinions of the authors are clear in the text, e.g., ". . . CDC has declined to perform . . . arguing nihilistically . . .," and comments on the "reluctance" of the VA show prejudice. Evaluation of attitudes toward the VA seems to indicate a political motive to the study. This is not appropriate for a scientific journal. The articles are rife with value-laden terminology and demonstrate a major lack of objectivity in interpretation.

The literature cited is not a complete summary of available data. Selective citation of references is evident throughout the reports. There is no attempt to differentiate between acute effects and long-term effects of exposure. The literature review does not discuss the differences between exposure of pregnant females and males. Repeatedly, pertinent and recent data were not cited or used.

Sincerely

William H. Wolfe

WILLIAM H. WOLFE, Colonel, USAF, MC
Chief, Epidemiology Division

COMMENTS ON THE STELLMAN STUDIES

Environmental Research 47, 109-111 (1988)

Editorial

Page	Para	Comment
----	----	There appears to be a limited editorial group,with 22% of those listed currently working at Mt. Sinai (13 of 58). I doubt the thoroughness of the peer review given to this series of articles.
109	3	Subjective opinions are clear in text that '...CDC has declined to perform.. arguing nihilisticly...' Study was halted when accurate assessment of exposure indicated that identifiable ground troops had no increase in TCDD
110	1	Ignores CDC ground troop validation-Published the month before these articles were submitted and 14 months before publication; allowing adequate time for revision
	3	Ignores the fact that all endpoints were 'reported'; none were verified.
	5	Comments on the 'reluctance' of the VA show prejudice; inaccurate statements are made without evidence
111	2	The measure of exposure is invalid by CDC work; data are unverified.

American Journal of Industrial Medicine 9:305-321 (1986)

Estimation of Exposure to Agent Orange

Page	Para	Comment
305	--	The probabalistic model is shown to be invalid by CDC work. This article was published before that work, but is now invalid. The indices are 'opportunity' indices, not 'exposure' indices. The use of 1 year half-life is probably too long in a non-soil environment.
306	2	The use of 'heavily' to characterize contamination is is very selective and ignores data on other species with different thresholds.
	3	The effects cited are primarily acute effects with the exception of choracne.
	4	The key question of 'exposure' is not validly addressed.
	5	Citation of AFHS data omitted caution that data on birth defects was not verified.
308	---	No attempt was made to validate the index or determine its accuracy. The index is basically the same as that used by the CDC. 309 1 The CDC index was more accurate, as it was based on records of troop locations and not on memory of place names 10 years later. 2 The use of a 15 km. area is excessive and fails to consider terrain effects and wind direction. Both are key to assessing actual exposure risk.
	3-5	Sophisticated math manipulations and formulae are only as good as the weakest data element. Therefore, the index in this study is worthless in light of lack of correlation between serum TCDD and troop locations and self-reported exposure by ground troops (CDC).
310	1	Use of memory to pinpoint location of duty is crude when relating to specific and far more accurate spray locations. 311 1 Six to 10 miles (10-15 km.) had to be used to get adequate number of subjects. Failure to account for terrain and wind make this an estimate of maximum likelihood and creates severe misclassification.
	3-5	No attempt was made to assess accuracy of the reported locations. Memory collected to month, but HERBS tapes to day and time. Authors doubt 'lying' affected the reporting. This does not make the reports accurate for placement in/near sprayed areas.

317 1 The fact that the index is similar to methods used in industry is not reassuring. Old studies are most likely as weak as this one.

320 1 The statement is made that the method is 'readily applied at minimal expense' is true, but it is not based on reality. It should not be confidently used in any studies. The AFHS index is probably more valid than this one, and it is being replaced due to its weaknesses.

Environmental Research Env Resrch 47, 112-128 (1988)

Combat and Herbicide Exposure

Page	Para	Comment
112	abst	Use of American Legion members could Combat and Herb Exp induce significant selection bias, due to differences between members and nonmembers. Authors cite a correlation coefficient of 0.24 as meaningful. This is at best only a weak relationship between combat and exposure to herbicides. This error of interpretation is seen throughout these reports. Authors had access to CDC data for more than a year but failed to use or cite the data in revisions of the manuscript.
	2	Authors are standing on a 'soapbox' using overstatements and ignoring contrary reports and data.
113	4	Evaluation of attitudes to VA seems to indicate a political motive to the study. This is not appropriate for a scientific journal.
114	3	Assumption that the index measures exposure to herbicides is incorrect.
115	2	Use of 'volunteer' researchers may generate bias in identification. There is no method of quality assurance of their work.
116		Same comments as on page 308-311 of AJIM.
117	2	The fact that two calculated indices are highly correlated (0.88) does make either one accurate or valid.
120	3	The 83 men who were herbicide handlers are the only ones in the study truly exposed. They represent only 4% of the studied group.
124	1	Mere proximity in time and space does not equate to actual exposure. 4 The use of Legionnaires raises the issue of significant selection bias since they are not representative of all Vietnam veterans. Authors demonstrate lack of participation bias between SEA and non-SEA vets but not between members and non-members. Do Vietnam vets join the Legion in different patterns than non-Vietnam vets? This issue is not addressed and could cause severe bias. Racial distribution is markedly different.

Environmental Research 47, 129-149 (1988)

Social and Behavioral Consequences

Page	Para	Comments
129	---	Article is rife with value-laden Social Consequencas terminology and demonstrates a major lack of objectivity in interpretation.
	abst	Scales for herbicide are not 'validated as stated. Some selection factors may account for some of the findings. The observed combat effects are clear, but it is unclear to what extent they are real or are influenced by selection bias. The statement on the interactive 'effect' with concurrent exposure to herbicides is not valid in the light of the deficiencies in the exposure index.
130	---	The literature cited is not a complete summary of available data. Selective citation of references is evident.
131	2	As previously noted, the index of exposure is quite weak.
132	---	None of the endpoints were verified by records review or examination. 133 2 Mere proximity over an extended time to a sprayed area does not equal exposure.
134	1	Blacks are underrepresented in the study. Only 1.5% vs at least 12% overall.
135	---	The study suggests that combat had some adverse effect, but the effect of selection bias is not considered or accounted for. The conclusions that income loss has occurred is not supportable from these data.
136-137		The analyses of outcomes with the exposure index are conspicuously absent.
138	2	These results could be biased by the patterns of membership in the Legion.
	4	The sophisticated exposure indices are essentially worthless in view of the lack of a relationship between probabalistic indices and actual exposures as measured by serum levels.
139	3	The statement that all measures are correlated with combat is false. All correlations are .30 or less, a level that shows poor correlation at best.

140	2	The fact that correlations were all statistically significant is irrelevant. The low p value is an artifact of large sample size and the sum of all pairwise relationships in the correlation matrix. This p value has no bearing on the validity of the correlations, with most showing only poor associations at best.
144	4	The use of manufactured data for an analysis of alcohol use should be deleted. The assumptions implicit in assumptions implicit in the calculation make it untenable.
147	1	The data on illicit drug use are likely to be seriously underreported. Data of this type must be collected by random response techniques to obtain reasonably accurate data.
148	---	The conclusions may be biased by the characteristics of Legion members. The interpretations of correlation coefficients is flawed (0.08 and 0.15 are NOT significant correlations). There is no discussion of the limitations of the exposure index, especially in view of 1987 CDC data. There was ample time for these data to be included or cited in this publication.

Environmental Research 47, 150-174 (1988)

Health and Reproductive Outcomes

Ppage	Para	Comments
150	---	There is heavy use of value-laden Health and Repro terminology in this paper. There is no mention of probable existence of differential reporting and its bias. abst The conclusions concerning herbicide exposure are unwarranted.
151	2-3	The literature review does not discuss the differences between exposure of pregnant females and males.
152	1	Pertinent and recent data were not cited or used.
153	---	None of the claims of exposure were validated and health endpoints were not verified.
154	1	Some endpoints such as 'skin rash with blisters' are unnecessarily vague, making interpretation hard.
	3	There is no attempt to differentiate between acute effects and l ongterm effects of exposure.
155	1	Pre SEA reproductive experiences were discounted. This is potentially an important confounder.
159	2	All correlations are misinterpreted. The p values only indicate a measure of pairwise variance of large sample sizes and not the validity of the correlations.
160	4	The index does not measure exposure to herbicides. It measures something else but what is not clear.
162	T	All correlations for year of birth, combat and 'Agent Orange' are poor.
163	2	Data on the variable 'child bearing attempts' is presented. What is the purpose of this variable? Why would Vietnam vets want to have more children? This appears to be a chance finding.
164	2	This finding may represent reporting bias, but the possibility is never considered.

166 2 Statement that 'Mean levels of Agent Orange exposure were ALWAYS significantly higher in ... miscarriage..' appears to highlight the effect of overreporting. This elevation in every case is highly unlikely. Surely some miscarriages occurred among occurred in women married to 'low' men.

170 2 Again, no verification was attempted.

Environmental Research 47, 175-192 (1988)

Post-traumatic Stress Disorder

Page	Para	Comments
175	---	This appears to be the best written of PTSD the series. It was clearly authored by a psychologist or psychiatrist.
179	1	Response bias is accounted for, but selection and reporting biases are generally ignored.
	2	The group under study is not representative of any group other than American Legion members (too many whites).
182	T	The numbers in the tables are not consistent (Tables 2-6).
190	3	This is the first mention of self reporting bias in the series.

Environmental Research 47, 193-209 (1988)

Utilization, Attitudes and Experiences

Page	Para	Comments
193	abst	Biased terminology is prevalent in VA this VA eport. The effect of the media and its effect on reporting is not considered.
196	1	The use of Legion representatives who work full-time in monitoring the VA to develop the questions is inappropriate. This likely injected bias in the questionnaire, as evidenced by the wording of the questions.
	7	The location of the questions about attitudes toward the VA before questions on health could have biased subsequent responses. The answer choices are unbalanced; 3 'true' choices and only 1 'false' choice.
198	2	Supporting data for the statement about major medical insurance and combat level are lacking.
202	T	Many of the questions are biased in wording. the use of words like 'fully' and 'all' are biasing. Veterans not needing pension or compensation services should not be expected to be 'very' knowledgeable about these programs. Many Questions ask for opinion about most' veterans; this is biased.
203	T	Only data for selected questions is presented in table and text. Where are results for other questions?
	3	In interpreting responses, 'slightly true' is interpreted as a negative response. Words such as 'considerable proportion' convey vagueness.
208	1	Use of 'particularly disturbing' is not objective, and should be reserved for an editorial. Bias of the author is clear.

Vietnam Era Veterans Study (Stellman et. al.) Questionnaire

The questions are generally superficial and the choices offered to the respondent are often poor, leading to potential sources of bias.

Data on locations of service in Vietnam are only 'accurate' to the month. This makes it difficult to relate veterans activities to daily spray missions.

Questions about attitudes toward the VA are generally biased in wording.

The health inventory is very cursory, vague in many areas and only covers 1 1/2 pages.

Questions on alcohol and smoking are so short that the data are probably unreliable for any reasonable analyses.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date December 23, 1988

From John F. Young, Ph.D.
Director, Division of Reproductive and Developmental Toxicology

Subject Review of articles from Environmental Research (47:112-209,1988) by Stellman et al.

To Dr. Vernon Houk
Chairman, AOWG Science Panel

OVERALL IMPRESSION:

A large study involving a lot of work which was fairly well done! The strong correlation between combat and Agent Orange (AO) exposures is not unexpected due to the way the study was conducted (self-reporting questionnaire); additionally, any correlation with combat status will also correlate with Agent Orange exposure. However, in light of the recently published CDC's TCDD serum data of Vietnam veterans (JAMA 260:1249-1254, 1988) which used similar procedures to identify the potentially highest AO exposure troops (including self reporting) and which indicated that actual AO exposure probably did not occur to any appreciable extent in any of the ground troops, the findings by Stellman et al. in relation to AO exposure has less significance.

The combat scale is inconsistent among the five papers. Why?
- Paper 1 - Fig. 4 & 6 -> 3 levels of low, medium, and high.
  Table 3 -> 5 levels of numerical scores.
  Fig. 5 -> 5 levels of lowest, low, medium, high, and highest.
- Paper 2 - 3 levels used throughout this paper
- Paper 3 - 3 levels in Tables 4 and 5
- Paper 4 - 3 categories different from all other papers -> median, 1 or more events, and all 8 events
- Paper 5 - Fig. 1,2,3 and Table 6 - 5 levels
  Fig. 4 - 2 levels of average or less and above average

SPECIFICS:

Paper 1: COMBAT AND HERBICIDE EXPOSURES IN VIETNAM AMONG A SAMPLE OF AMERICAN LEGIONNAIRES. Environ Res 47: 112-128, 1988.

1) Fig. 2 - Are the Orange and White labels reversed? It would appear to be reversed if Figure 1 is correct with the usage amount of AO about twice that of Agent White.

2) Table 2 - How were the 95% confidence intervals calculated? According to the text (page 120, 2nd paragraph), the herbicide exposure index OE3 mean was 0.357 with a standard deviation of 0.752 which would translate into a 95% CI (+/- 2 SD) of 0-1.861. However, the table has a 95% CI of 0.32-0.39. I wonder about the rest that can not be checked.

3) The combat ranking scale varied from Table to Table or Figure; e.g., Table 3 has 5 levels of combat scores, Figure 5 has 5 levels of lowest, low, medium, high, and highest, and Figure 6 has 3 levels of low, medium, and high. How do these various rating scales interrelate? Is the "lowest" in Figure 5 the same as the score of 8-10 in Table 3? Is the "low" in Figure 6 the same as the "low" in Figure 5 or is it equivalent to the "low + lowest" in Figure 5?

4) In a paper describing a procedure of picking cohorts, it would be of interest to see the responder characteristics between the Vietnam veteran and the non-Vietnam veteran (the two comparison groups). Instead the authors chose to present the responses between two States (Table 4). Isn't this trivial information that skirts the main issue of comparison?

5) In general it would have been informative if the authors had presented the actual logistical information of total number of members of the 6 American Legion state organizations, number of postcards sent out and returned, number of questionnaires sent out and returned, and complete demographic information on the two cohorts.

Paper 2: SOCIAL AND BEHAVIORAL CONSEQUENCES OF THE VIETNAM EXPERIENCE AMONG AMERICAN LEGIONNAIRES. Environ Res 47:129-149, 1988

1) The authors stated that education was predictive of income (p. 134, last paragraph) and that income was inversely related to combat level (Fig. 1). Is there any information from the available literature that would indicate that lower educated troops were more often used in the more intense combat areas? Does the "pre-Vietnam" educational level also correlate inversely with combat level?

2) I doubt the significance of the data in Table 3. I find it hard to believe that a mean income difference of ~$3000 will be statistically significant (Table 3) or that the bars in Fig. 1 are really the 95% CI. If we take the data from Fig. 1 for "Not SEA", the 95% CI would include incomes of between $20,000 and $21,000; using Table 2, 95% of the "Served elsewhere" group would have an upper income of $21,000 and a lower income of $20,000. Therefore only about half of the graduate/professional school group would be earning over $21,000 and only half of the group with less than a high school education are earning less than $20,000. I don't believe this is reasonable. It may be a minor point, but what does it mean in relation to the rest of the numbers that are presented as means and 95% CI that can not be checked.

3) The authors also state in regards to this same data that "These findings demonstrate that significant family income loss has, on the average, occurred among Vietnam combat veterans, irrespective of their degree of educational attainment." (p. 135, first sentence of last paragraph). They do not present the data to substantiate this statement.

4) Table 4 - How do they calculate the odds ratios? I don't understand how they can calculate a "p" value from count data. What is used for the variance? It would have been helpful if the authors had chosen to present their statistical treatment procedures.

5) On page 148, first paragraph, the authors state that "... there is an over-representation, by design, of men with combat zone experience, ...". What is this based on and how was it done? There are more non-SEA persons than Vietnam veterans in the total study, there are more persons in the low combat category than the high, and the level of combat experience was only obtained after the questionnaire was returned. Therefore how or what was done "by design".

Paper 3: HEALTH AND REPRODUCTIVE OUTCOMES AMONG AMERICAN LEGIONNAIRES IN RELATION TO COMBAT AND HERBICIDE EXPOSURE IN VIETNAM. Environ Res 47:150-174, 1988

1) In the other 4 papers in this series, the measured parameter of interest is correlated to combat level and then to Agent Orange. In most cases the effect of AO is minimal due to the strong correlation that was obtained between combat and AO. Therefore the culprit was "combat" that caused all of the problems. However, in this paper the authors have reversed the order of regression with AO being the primary culprit and combat taking the secondary role. Why have they taken this approach and changed their mode of statistical evaluations?

2) Table 1 - It is interesting to note that in every instance, the Vietnam veteran had a higher incidence of the disease or condition. Might not this indicate that the Non-SEA person was less likely to report a malady than the Vietnam veteran? Why was cancer (especially Non-Hodgkin's lymphoma or soft-tissue sarcomas) not included on the list of medically diagnosed diseases? That is the area that has received the most press for a number of years.

3) On page 162, the authors explain that birth defects data is not included because it is necessary to have medical verification for such findings. Why is verification of the other medical diagnosis not necessary?

4) Page 166, 2nd paragraph: Where is the data to support the authors' statement "Mean levels of Agent Orange exposure were always significantly higher in pregnancies which ended in miscarriage, compared to those that ended in live births, ...".

5) There is a general lack of a real discussion section in this paper. The literature is discussed but the "data" presented in this paper is not discussed.

Paper 4: POST-TRAUMATIC STRESS DISORDER AMONG AMERICAN LEGIONNAIRES IN RELATION TO COMBAT EXPERIENCE IN VIETNAM: ASSOCIATED AND CONTRIBUTING FACTORS. Environ Res 47:175-192, 1988

1) Page 190, 2nd paragraph: The authors state that PTSD-like symptoms were found in veterans not considered to be exposed to heavy combat, yet no data was presented to compare the Vietnam veteran to the "no combat" Non-SEA group. The data was apparently available to make such a comparison.

2) AO is not discussed in this or the final paper, even as a potential interaction element, as was done in the first two papers. I wonder why?

Paper 5: UTILIZATION, ATTITUDES, AND EXPERIENCES OF VIETNAM ERA VETERANS WITH VETERANS ADMINISTRATION HEALTH FACILITIES: THE AMERICAN LEGION EXPERIENCE. Environ Res 47:193-209, 1988

1) I didn't find anything really surprising in this paper other than there was no comparison to the AO exposure level.

EDITORIAL: NEW LIGHT ON THE HEALTH OF VIETNAM VETERANS. Michael Gochfeld. Environ Res 47:109-111, 1988

The author indicates his bias very early in the editorial with the statement concerning the "remarkably complacent responses" of the DoD and VA. Later in the article he refers to the VA's role with terms such as "with much reluctance", "of varying reliability", and "the VA's inadequate role".

He also makes a much bigger point of the role of AO in the statistical analyses of the 5 papers than is actually found in the data. Mr. Gochfeld does indicate the value of TCDD blood levels as a biomarker for AO exposure, but does not follow through with the logical inclusion of a reference to the CDC work; perhaps a problem with timing. In light of the CDC JAMA article, I do not agree with Mr. Gochfeld or the Stellman et al. articles that "categorization of Vietnam veterans according to herbicide exposure can be successfully accomplished".

Unfortunately, the editorial put too little emphasis on the main issue of combat level related issues in the obvious desire to over implicate the weaker role of Agent Orange exposure.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
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Occupational Safety & Health
Robert A. Taft Laboratories
4676 Columbia Parkway
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December 30, 1988

Vernon Houk, M.D.
Director, Center for Environmental
Health and Injury Control
Centers for Disease Control
Bldg. 27, Room 1213
4770 Buford Highway
Atlanta, GA 30341

Dear Dr. Houk:

In response to your letter of November 22, 1988, please find enclosed our review of three papers by Stellman et al, 1988 one paper by Snow et al, 1988, and the editorial by Michael Gochfeld, which are based on a single study conducted on a sample of American Legionnaires. The review was completed by Marie Haring Sweeney, Teresa Schnorr, Ph.D., Victoria Wells, M.D., Ph.D., and Marilyn Fingerhut, Ph.D. Each paper is reviewed separately. A summary of our findings is presented here:

This largely negative study of a sample of American Legionnaires, who served in Vietnam and in other areas, does not confirm that experience in Vietnam caused serious health or reproductive effects among the sample of Vietnam veterans compared to non-Vietnam veterans. Serious methodological limitations include incomplete ascertainment of the target sample, lack of verification of self-reported health conditions and reproductive events, inadequate control of risk factors such as smoking and other factors in the analysis of health outcomes, and absence of adjustment for multiple comparisons. The limitations require that the few positive findings be interpreted cautiously.

The detailed reviews of each article are enclosed.

Sincerely yours,

Marilyn Fingerhut

for

Marie Haring Sweeney
Chief, Dioxin Activity
Industrywide Studies Branch
Division of Surveillance, Hazard
Evaluations and Field Studies

Enclosure

"Combat and herbicide exposures in Vietnam among a sample of American Legionnaires." Stellman S, Stellman JM, Sommer JF. Environmental Research 47, 112-128 (1988).

This paper presents a brief description of methods used to estimate exposure to Agent Orange using a "probabilistic exposure index" based on information on spray missions carried out in Vietnam (date of application, herbicide type and coordinates of application) and methods to calculate level of combat experience. Methods for selection of the study population and the resulting participation rate were also discussed.

Selection of study population, data collection methods and participation rate: Major concerns include biases introduced due to possibly incomplete ascertainment of the target population, the data collection methodology of a mailed questionnaire, and the low participation rates.

Population selection: The study population was composed of members of the American Legion in six states who had been members for less than 20 years as of 10/1/83. Selection bias and the problem of non-representativeness of the study population are inherent in this type of study because the subjects are self-selected as members of the American Legion, thus omitting non-member Vietnam and Vietnam-era veterans. This study is unlike the CDC study which included a sample of all living Army veterans. Yet like the CDC study, the design is cross-sectional, omitting those who died prior to the study. The Stellman study (1988) also excludes members who let their membership lapse.

A particular concern of this study is the potential inability to identify the entire target population. It is not clear from the text that all Vietnam and Vietnam-era veterans fitting the inclusion criteria of the sample were identified and asked to participate in the study. If the entire target population was not requested to participate, the results would not be representative of the membership of the American Legion, nor the Vietnam veteran population. For example, if those who responded were members worried about combat-related or Agent Orange exposure and their current health, the results would be biased.

Data collection methods: All data were collected using self-administered questionnaires. No verification of self-reported health effects was conducted. This issue is particularly a problem for interpretation of self-reported medical conditions and reproductive events and, therefore, is discussed in the review of "Health and Reproductive Outcomes among American Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam."

Participation rate: The text does not state the exact response rate for each state. The report indicates that participation ranged from 52.5% to 64.1%, suggesting that participation of those contacted was low.

The method for assessing response bias appears reasonable for description of the respondents, but it is also important to determine the characteristics of the nonrespondents and whether or not the nonrespondents were similar in health and exposure parameters to those who participated. A characterization of non-respondents was not discussed.

Exposure assessment: The authors state that they "provide an analysis of patterns of exposure of American Legionnaires to various levels of ... herbicides". Actually, they utilize their 1986 exposure indices which calculate proximity (within 15 km) between the location self-reported by the participants to the location of herbicide sprays obtained from the Air Force HERBS tapes and related documents.

Unfortunately, the authors failed to discuss the validation study conducted by the CDC to test the adequacy of a similar exposure system based upon the HERBS tapes, even thought they were aware of the study. The validation study, required by the Office of Technology Assessment of the Congress, demonstrated conclusively that there was no association between the exposure levels predicted by the proximity of geographic location of troops with location of herbicides sprays as documented on the Air Force HERBS tapes. It is standard procedure for researchers to point out how their methods and results compare with others. The failure of the authors to explain why they consider their method to be valid in light of the demonstration of the CDC that a similar effort was proven incorrect leads to a worrisome concern about lack of objectivity in conducting the research or writing the paper. We would have preferred to see the authors propose that their system be tested in a similar fashion. Instead, they conclude that they have provided "a readily used and inexpensive exposure classification system", even though they have not tested its accuracy in any way nor have they pointed out the clear failure of a very similar system designed with at least equivalent care and effort by the CDC.

Social and behavioral consequences of the Vietnam experience among American Legionnaires. Stellman JM, Stellman SD, Sommer JF. Environmental Research 47:129-149 (1988)

This paper reviewed demographics, smoking and alcohol consumption patterns and social and behavioral parameters among the studied sample of Legionnaires.

Demographic characteristics and personal habits: The study population was composed of all males and was 98.5% white. This is in contrast to the Army veterans studied by CDC who were 83.2% white males. Among the Legionnaires, there was no difference in the level of education achieved between Vietnam and non-Vietnam veterans. When comparing the Legionnaire data to the CDC cohort, 6.3% of the Vietnam veterans and 5.5% of the non-Vietnam veterans achieved less than a high school education while in the CDC cohort, 14.1% of the Vietnam veterans and 11.6% of the non-Vietnam veterans did not graduate from high school. These data suggest that the Legionnaires tend to be more highly educated than other groups of veterans.

Social and behavioral functioning: The report concluded that social and behavioral functioning, such as sexual satisfaction and marital stability, diminish with increasing exposure to combat. The arguments are presented clearly. Unfortunately, some factors which may predispose individuals to increasing combat level and the outcomes under study, e.g., personality characteristics developed prior to service, are not fully studied. The Card (1980) study claims that the men who served in Vietnam were "comparable to their peers who did not...(serve in Vietnam)," but it seems likely that unmeasured (and perhaps often unmeasurable) factors might lead to "increased combat exposure," and "social dysfunctioning."

Likelihood of exposure to Agent Orange was "statistically associated" with two behavioral outcomes, anxiety and physical depression. However, when "exposure to combat" was added to the model, these associations were not statistically significant. The authors conclude that the effects of herbicides on psychosocial well-being should be studied only with "exposure to combat" as a potential confounder. It is our opinion, that based on the results of the CDC serum 2,3,7,8-TCDD validation study, there is little evidence of exposure for the majority of the veterans stationed in Vietnam. Since the results of the CDC study were available to the researchers, it is surprising that their discussion include a recognition of this information. The results of this study implicate combat intensity as a contributor to increased social dysfunctioning.

Health and Reproductive Outcomes among American Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam. Stellman S, Stellman JM, Sommer JF. Environmental Research 47:150-174 (1988).

A. Health effects other than reproductive:

The study found generally negative results for most self-reported conditions which the authors describe as endpoints of exposure to phenoxy herbicides or TCDD. Interpretation of the few statistically significant excess risks among veterans stationed in Vietnam compared to non-Vietnam veterans is severely limited due to possible selection biases. The limitations of the health data are as follows:

1) Questionnaire construction: Many of the outcomes collected in the questionnaire are confined to broad classifications of diseases e.g., heart disease, genito-urinary problems or nervous system disease, rather than specific conditions. Information on specific conditions was not solicited. Collection only of broad classes of conditions is not appropriate because the relevant literature does not associate every disease within a broad classification with exposure to phenoxy herbicides. A better method would have been to collect the names of the specific conditions and then combined related effects in the analysis. In addition, some of the questions ask for past occurrences of unrelated conditions, which may lead to erroneous conclusions. For example, the article defines sebaceous cysts as an example of benign fatty tumors. Sebaceous cyst have been described in workers diagnosed with chloracne, however, according to our consulting dermatologist, sebaceous cysts are quite rare and they are not considered to be benign fatty tumors. Therefore, the excess of benign fatty tumors described among Vietnam veterans with "the potential for high Agent Orange exposure" may be an artifact of incorrect question construction.

2) Risk Factors: An extremely important omission in the text is the lack of discussion about which confounders or other risk factors were included in the assessment of the reported conditions. For example, the risk for heart disease was adjusted for age, but there is no mention that the analysis was adjusted for smoking, high blood pressure, obesity or other factors which are well-known risk factors for many types of heart disease. Information on smoking and current weight and height was collected in the questionnaire and could have easily been introduced into the analysis.

Several skin conditions were also reported in excess among Vietnam veterans compared to non-Vietnam veterans. These conditions may also be related to exogenous or endogenous factors including medications, allergies, chemical exposures, none of which were quantified or controlled for in this study.

3) Confirmation of self-reported conditions and symptoms: All of the information collected on each health outcome and symptom was self-reported in a mailed questionnaire. None of the conditions were confirmed by examination of records documenting such events. Although validation of self-reported events is an arduous task, it is necessary to assess and control for the possibility of recall and reporting biases in the study groups. Previous

studies have documented that individuals with a disease of interest or with exposure to a substance under investigation, have heightened recall of events compared to controls without the disease or the exposure. For example, the four skin conditions asked about in the questionnaire were found to be statistically significantly elevated among Vietnam veterans. These conditions have been repeatedly reported in the scientific literature and popular press to be associated with exposure to dioxin-contaminated materials, particularly in exposed occupational populations. This coverage could have influenced the responses of the subjects.

Reporting bias may also be a problem if there is not a consensus on the interpretation of each question by the targeted responders. Short of employing trained interviewers to administer the questionnaires, review of clinical records would help to confirm the diagnosis of the self-reported events. Without any type of confirmatory data, it is not possible to rule out the possibility that positive findings are the result of reporting and recall bias.

4) Another major concern regarding this study is the lack of documentation of other exposures, particularly occupational, which are related to the health outcomes of interest and which may have occurred during the 20 years between the veteran's tour in Vietnam and his participation in the study. Many other chemicals and physical agents cause health effects which are also associated with exposure to dioxin-contaminated materials. The omission of this information is a serious flaw in the design of the study.

5) There are many statistical tests conducted on this data set. However, there was no mention that corrections were made to correct for the multiple comparisons problem.

Summary: The health effects reported in this paper are generally negative, although some conditions were reported in excess among Vietnam veterans. The quality of the self-reported data are suspect because they were not confirmed with more objective data, such as information from medical care providers. Outcomes found in excess among Vietnam veterans compared to non-Vietnam veterans must be interpreted cautiously due to the absence from the models of risk factors other than the exposure and combat indices.

B. Reproductive Outcomes:

In the reproductive component of the study, there is not sufficient detail in the report to permit us to draw meaningful conclusions regarding reproductive effects. The descriptions of the study methods and the analytic techniques omit critical details. These are enumerated below:

1) The response rate was apparently quite low. Of the 12,588 Vietnam veterans mailed a questionnaire (Stellman preliminary report) only 6,810 (54%) responded.

2) The study population for the reproductive outcome analysis is not well described. In Table 9, a total of 3,372 men are reported to have had or tried to have children. In "the Delay in Fathering" analysis, 3,078 men

were included in the analysis. This was 294 fewer men, presumably because 294 men had fathered a pregnancy prior to Vietnam service. In the miscarriage analysis, 2,950 men were analysed. This number is 128 fewer than the number given for the Delay in Fathering Analysis but no explanation is given for the difference.

3) There is some concern about the validity of the outcome data for three reasons. 1) The data on the outcomes of pregnancies were obtained from men, not the women. Other studies have shown men to be poor informants regarding their wives' pregnancy outcomes. 2) The data were obtained by a mailed questionnaire, which is less detailed or complete than other administered questionnaires. 3) The pregnancy outcome responses were not validated with medical records, so the potential for differential recall cannot be evaluated.

4) All pregnancies were included in the analysis. Inclusion of all pregnancies can lead to a biased estimate since the pregnancies of an individual woman are not independent events. In the analytic technique used, a single woman could have contributed many miscarriages to the data set. The authors do not discuss this issue and did not attempt to control for this factor in the analysis.

5) Factors such as parity and prior spontaneous abortion are important risk factors for spontaneous abortion. However, these factors were not considered in the analysis.

6) It appears from the questionnaire that date of the pregnancy and date of Vietnam service were available for consideration in the analysis. An analysis of miscarriage by time since Vietnam service would have been useful in interpreting the findings.

7) The question used to determine whether the veterans had difficulty having children was phrased rather vaguely "Have you ever experienced difficulty in having children?". A more objective definition such as "Did you ever try to have a child for at least one year but were unable to?" would have been more likely to be interpreted uniformly by respondents.

Summary: Given the limitation in the data collection and analyses, at this time, it is difficult to agree with the authors' conclusions that miscarriages showed a dose-related risk with Agent Orange exposure.

8

Post-traumatic stress disorder among American Legionnaires in relation to combat experience in Vietnam: associated and contributing factors. Snow BR, Stellman JM, Stellman SD, Sommer JF. Environmental Research 47: 175-192 (1988).

Of the four papers in the series, this one has the best organization and clearest presentation; the hypotheses and objectives of the analyses were stated clearly, and the results were to the point. The authors state that the instruments used to assess post-traumatic stress syndrome (PRSD) included a list of symptoms from the DSM-III and a combat scale, which had been validated in previous studies. The data indicate that individuals with exposure to eight or more combat events report more of the symptoms consistent with PTSD and that a higher combat score is directly related to higher PTSD intensity scores. According to one definition of PTSD, the percent of participants in this study reporting symptoms consistent with a diagnosis of PTSD (15%) was similar to the percent of Army veterans in the CDC study who had met the diagnostic criteria for PTSD at some time during or after service (15%).

Summary: This article shows that some veterans in this sample demonstrate symptoms which are consistent with PTSD. Although the authors state that the subjects were a "random sample" of Legionnaires, the first paper in the series points out the volunteer nature of the participation. Therefore, it is not possible to know whether or not the nonrespondents experience the same pattern of symptoms as respondents.

Editorial: "New Light on the Health of Vietnam Veterans" by Michael Gochfeld.

Although this editorial may have been written prior to the 1988 JAMA publication of the results of the CDC validation study, the MMWR carried the information in 1987, and the data were presented in October, 1987 at the Seventh International Symposium on Dioxin in Las Vegas. Dr. Gochfeld omits a description of the CDC study, although he clearly supports the concept that "measurement of TCDD levels in blood is a feasible biologic marker of past exposure to dioxin..." and that "...such a surrogate may be utilized as an index of exposure...". It is our opinion that the CDC validation study clearly demonstrated that there was not substantial exposure to Agent Orange among the ground troops in Vietnam. Failure to compare the two exposure systems in the editorial leaves the reader without a critical evaluation of them.

Dr. Gochfeld refers to the conclusion (drawn justifiably, in our opinion) to cancel the CDC study of Agent Orange-exposed veterans and he agrees that the CDC validation study had demonstrated that "only a minority of veterans had appreciable herbicide exposure". That validation study also demonstrated that the HERBS tapes failed to predict exposure levels which correlated with levels of dioxin in veterans. Consequently, we disagree with Dr. Gochfeld's statement that the present paper explains how to avoid the misclassification of exposure in prior studies. We suggest that the authors follow the CDC example and test their exposure-system by evaluation of dioxin levels in a sample of veterans identified as having high, medium, and low levels of exposure to Agent Orange. Until they have demonstrated that their system is accurate, it should be assumed to have the same flaws as the system ultimately rejected by CDC.

The editorial also misses the opportunity to explain the epidemiologic pitfalls of the study, including selection and reporting biases and non-representativeness of the sample. This would have been a perfect chance to educate the interested public in the problems associated with cross-sectional studies . However, the author does point out of the limitations of reconstructed exposure histories and the inherent biases of exposure misclassification.

With regard to health effects, the author suggests that the "health effects data actually confirm some fears" but he does not explain that the report reflects the opinions of the sampled veterans about their health because there was no confirmation of the accumulated data, and, therefore, the results of the study must be interpreted cautiously.

Department of Medicine and Surgery
Washington D.C. 20420

Veterans Administration

DEC 2 1988

In Reply Refer To:

Vernon N. Houk, M.D.
Director, Center for Environmental
Health and Injury Control
Centers for Disease Control
Atlanta, Georgia 30333

Dear Dr. Houk:

As requested, enclosed are comments prepared by myself and Dr. Han K. Kang on the recently completed American Legion studies.

If you have any questions regarding our comments prior to the January 10, 1989, meeting of the Agent Orange Working Group Science Panel please feel free to call me at FTS 373-3064/4117. Dr. Kang can be reached at (202) 634-4600.

Sincerely,

LAWRENCE B. HOBSON, M.D.
Director, Environmental Medicine Office

DEPARTMENT OF MEDICINE AND SURGERY
ENVIRONMENTAL MEDICINE OFFICE

AMERICAN LEGION STUDIES ON HEALTH OF VIETNAM VETERANS

1. The studies by Stellman and Stellmen for the American Legion have produced a paper on methodology (AM. J. Industr. Med. 9:305-321. 1986) and a series of five papers on results (Envir. Research. 47:112-209. 1988). The latter series also contains an editorial by Gochfeld.

2. The entire effort depended on self-reporting by 6,810 American Legion members who are Vietnam era veterans and 2,860 of whom served in "Southeast Asia." Each subject received a questionnaire asking about his service in Vietnam, medical and psychological status, reproductive history, socioeconomic factors, and attitude toward the Veterans Administration. The questionnaire required some one and a half hours to complete and the American Legion assigned a "volunteer researcher" to each subject to ensure a high compliance rate. The investigators believe, but without evidence, that this did not influence responses to the questions.

3. Copies of the questionnaire have not been supplied on request, but some details are mentioned in the papers. The form asked whether a doctor had informed the veteran that he had one or more of 23 diseases (not listed in the paper) and also 28 "health conditions currently a problem" (also unlisted). In addition, specific questions were asked about acne, skin rash with blisters, changes in skin color, and a part of the body becoming more sensitive to light. These are said to have been "questionnaire derived."

4. Exposure to Agent Orange was calculated by a somewhat complex formula that depended on the veteran's locating himself in Vietnam. To do so he was given a list of at least 98 place names with a map and asked at which and on what dates he served there. Information from the HERBS tapes was used to locate spraying. The evaluation method is essentially the same as that tried and discarded by the AOWG Science Panel, Office of Technology Assessment, the VA, and the Centers for Disease Control. It has numerous serious defects and now has been shown to be useless by the finding of no exposure among ground troops by blood assays for 2,3,7,8,-TCDD even for such veterans whose supposed contact with Agent Orange was calculated to be great.

5. Combat experience was judged by response to eight questions. No attempt was made to validate the answers by comparing with military records, i.e. assignment to companies, correlation with company records of location, military specialities, and special duties.

6. Results, especially physical and mental health, are reported in a confusing fashion, especially in respect to a causal relation distinguishing between Agent Orange exposure and combat stress. Thus heart disease is sometimes included among the effects of Agent Orange and at other times is specifically excluded. In most places, the health effects of herbicides are given as four: skin rash with blisters; adult acne; increased sensitivity to light, and benign fatty tumors. The latter are reported as including sebaceous cysts, not properly so considered. Veterans who had actually

handled herbicides were said to have had more cases of hypertension and gastric or intestinal ulcers. Wives of veterans who were said to be exposed to Agent Orange were reported to have had greater risk of miscarriages.

7. Truly serious physical diseases, such as epilepsy, ulcerative colitis, and Addison's disease, had too few occurrences to be correlated and some, such as kidney disease and diabetes, occurred uniformly in various groups. Other medical conditions were said to be related to service in "Southeast Asia," e.g., heart disease, without ascription to a specific cause.

8. Combat stress was found to be dose-related to hypertension, ulcers, fatty tumors, arthritis, G-U problems, and major accidents. There was also an increasing prevalence of post traumatic stress disorder with an increasing level of combat, as judged from the questionnaires. Among 28 percent of veterans with higher combat stress, 15 percent reported PTSD according to the definition used.

9. Questions about relationships with the VA where biased in several instances, e.g. "I have been fully informed about the availability of an Agent Orange examination at the VA." Results included a lower level of knowledge about the VA and more negative attitudes toward the VA among veterans who had never used the VA. Emphasis was given to the failure of VA facilities to ask questions relevant to PTSD and about combat experiences.

10. The questionnaire survey was completed in 1984. No mention is made of Vet Centers, nor of the VA registry, of recent research, of late Air Force reports on Ranch Hand studies. The CDC blood level experience is completely ignored.

11. In view of the technical flaws, of the lack of reference to recent research, and the trivial nature of the health effects attributed to exposure to Agent Orange, the Stellmans' reports hardly justify the statement that the findings are of major importance or indicate serious health defects resulting from exposure to Agent Orange.

LBHOBSON 12/5/88

A REVIEW OF THE AMERICAN LEGION STUDIES PUBLISHED IN ENVIRONMENTAL RESEARCH

I. Editorial "New Light on the Health of Vietnam Veterans"

The editorial points out "only a minority of veterans had appreciable herbicide exposure." No one seems to disagree on this point. The question that everyone is struggling with is how to identify them within the limits of resources and time. The Stellman et al paper simply presents another way to classify Vietnam veterans based on military records without any evidence that their classification method is reliable. The CDC validation study demonstrated convincingly that military records alone are not a sufficient basis for the categorization of Vietnam veterans according to their probable Agent Orange exposure. The editorial did not mention the CDC study.

Dr. Grochfeld seems to favor the use of a surrogate measurement, TCDD levels in blood, as an index of the exposure and as a basis for analytical stratification. However, it is not conceivable to apply this invasive, costly procedure to all of the 3 to 4.4 million veterans who served in Southeast Asia.

Granted this is an editorial, but some phrases are inflammatory and not substantiated. For example, "remarkably complacent responses" referring to the VA and the DOD, "a dearth of well designed studies"discussing scientific evidence , "arguing nihilistically" describing the CDC, " with much reluctance" and "of varying reliability" characterizing the VA Agent Orange Registry Program.

Contrary to the editorial, the VA has provided priority medical care to all Vietnam veterans under PL 97-92,99-166 without regard to the veteran's age, service-connected status or the veteran's ability to pay for the expense of such care. Almost all Vietnam veterans who may have been exposed to Agent Orange are eligible for medical care under this program except those veterans presenting the following types of conditions that are not ordinarily considered to be due to Agent Orange exposure: 1. congenital defects; 2. conditions which are known to have pre-existed military service; 3. conditions resulting from trauma; 4. conditions having a special and well established etiology. This priority treatment program has been in existence for 6 years (not 2 years) and a total of 1.3 million outpatient visits and 25,000 in patient treatments have been made under this program. These figures indicate that the eligibility requirement for medical care is not as stringent as the editorial suggested.

II. Combat and Herbicide Exposures in Vietnam Among a Sample of American Legionnaires

This paper describes two critical methods for determining

the likelihood of exposure to Agent Orange and the extent of combat experience based on military records or self-reported data. Analyses and interpretation of the subsequent four papers very much hinge on the validity and reliability of these methods. The paper fails to present any convincing evidence that both methods are valid and reliable. The fact that "a large proportion of men whose likelihood of herbicide exposure was either nil or low, while a sizeable number of individuals were classified as high exposure" is not by itself evidence that the method is valid. This may be a simple reflection that herbicides were not applied uniformly throughout South Vietnam. Furthermore, "that health-related effects to be presented in the successor paper of this paper often display a dose-response relationship with respect to herbicide exposure" may be resulting from selective recall of veterans who may have various health conditions. The results of the study would have been more convincing had there been some effort to validate questionnaire data against readily available military personnel records and medical records.

No reference or discussion was made concerning the CDC validation study which indicated no matter how one uses military records to classify exposure likelihood, classification based on military records is not supported by TCDD levels in blood.

Aside from the lack of validation, there is no evidence that an internal consistence in responses was carefully checked. There are some questions I would like to ask.

1. What is the definition of Vietnam Era in this study?
2. How many veterans selected for the study by the "volunteer researchers" were found not meeting the eligibility criteria after questionnaires were completed?
3. How many veterans served in Cambodia or Laos? what was their Agent Orange exposure classification? What were their stated health problems? To my knowledge HERB tape and Services HERB tape do not contain data on use of herbicide in Cambodia or Laos. Therefore, veterans who served in either country should have been classified as no or minimum exposure unless they handled herbicides.
4. One out of 10 veterans who served in non Southeast Asia were classified as having levels of combat ranging from 11 to 15. Were they mostly career type veterans whose military service dates included a period of other war? If not, can their stated combat exposure away from hostile enemy activities in Southeast Asia be explained?

III. Social and Behavioral Consequences of the Vietnam Experience Among American Legionnaires

The entire report is based on questionnaire data without a single item being checked for accuracy or a systematic bias. How does one rule out the possibility of selective recall among those veterans experiencing social and behavioral problems? Although the effects of combat experience on social and behavioral outcomes are plausible, erroneous findings can not be ruled out. When there is substantial difference in the marital status of these two groups (Vietnam and non Vietnam veterans), family income rather than veterans' income may not be an appropriate measure of socio-economic status of veterans.

IV. Health and Reproductive Outcome Among Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam.

Lack of any attempt to validate data on both outcome variables and independent variables is again of major concern in the report. Notwithstanding this concern, the observation that only one medical condition (benign fatty tumors) was associated with Agent Orange exposure provides a sense of relief. With respect to reproductive outcomes, it should be noted that male veterans were asked family reproductive histories rather than their wives. On page 152, the Hoffman et al (1986) paper was cited for "statistically significant differences in immune system response". It should be noted, however, that in a later year the authors reported the failure to confirm depressed delayed-type hypersensitivity skin test reactions in the TCDD-exposed cohort. (Dioxins 87, October, 1987).

V. Post-traumatic Stress Disorder Among American Legionnaires in Relation to Combat Experience in Vietnam: Association and Contributing Factors.

The existence and elevated rate of PTSD among Vietnam veterans are certainly plausible but the lack of validation of combat experience makes the finding less convincing. It should be noted that the prevalence of PTSD can range from 1.8% to 15.0% depending on the definition of evidence of exposure to a traumatic event.

VI. Utilization, Attitudes, and Experiences of Vietnam Era Veterans with Veterans Administration Health Facilities: The American Legion Experience.

There seems to be a gross misconception of the role of the VA in providing medical care to veterans. The VA under the law provides medical care (both in patient and out patient) primarily to veterans with service connected health problems. If beds are available services are provided to other veterans. In other words, the VA is not authorized to provide free medical care to all veterans.

Several questions were asked which would likely generate negative responses. For example, 1) the lifetime health benefits of the VA were a strong incentive to me to join the service; 2) in an emergency situation I would prefer to go to a VA facility than to a community hospital; 3) the VA system is a good, secure alternative for me for health care needs in the future; and 4) the VA system provides security and peace of mind to most Vietnam era veterans.

Some questions were phrased in such a way that answers would be almost always "not true". Examples are 1) I am fully aware of all the benefits...;2) I am very knowledgeable...'3) I am aware of the workings of the...; and 4) I have been fully informed about the availability of.., One question seems to ask other veterans' perceptions rather than the respondent's, i.e. Most Vietnam era veterans feel very positive about the VA. It is encouraging that the majority of those who used the VA have expressed a great deal of satisfaction toward their experience.

In conclusion, I do not find much fault in the mechanical handling of data that has been collected. Statistical tests seem appropriate and interpretation seems reasonable. However, they fail in one crucial area: no attempt was made to validate any of the data items they collected. If one starts out with invalid data, no amount of statistical manipulation will make it right.

HAN K. KANG, Dr. P.H.
Veterans Administration
Office of Environmental Epidemiology

December, 1988

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, D.C. 20301

HEALTH AFFAIRS

06 JAN 1989

Vernon N. Houk, M.D.
Chairman, Science Panel,
Agent Orange Working Group
Centers for Disease Control
1600 Clifton Road, NE (F29)
Atlanta, GA 30333

Dear Dr. Houk:

I have read the studies published in Environmental Research. I believe the major discrepancy in this study is the fact that they have no objective evidence of exposure such as serum dioxin. Since the CDC has demonstrated that with serum measurements you cannot distinguish a group defined as exposed from a group defined as not exposed using military records, any studies subsequent to that would not have as much weight as they might prior to availability of that objective evidence. While there are a number of specific areas in the selection of the population, the method in which the individuals were questioned, and the use of a select group such as the American Legion, these deficiencies can be seen in other epidemiological studies as well. Without an objective measure, describing the minimal effects observed as dose-related overstates the case.

Dr. Jerome Bricker has also reviewed this information. Since his experience in the analysis of spray patterns and the HERBS data set is so extensive, I am including his complete analysis of the American Journal of Industrial Medicine article.

Sincerely yours,

David E. Uddin
CAPT, MSC, USN
Senior Policy Analyst
for Medical Research

Review Prepared by Dr. Jerome Bricker

1. "Combat and Herbicide Exposures in Vietnam among a Sample of American Legionnaires," by S.D. Stellman, J.M Stellman and J.F. Sommer, Jr.

Since the conclusions in this and subsequent articles in the series concerning Vietnam veterans exposure to Herbicide Orange are based on the original methodology proposed by the authors in the 1986 article entitled "Estimation of Exposure to Agent Orange and Other Defoliants Among American Troops in Vietnam: A Methodological Approacn" published in the American Journal of Industrial Medicine 9:305-321 (1986) it is necessary to first point out the potential problems believed to exist in the exposure estimation methodology. In the introduction the authors state that the 2,4,5-T used as Herbicide Orange was heavily contaminated with TCDD with a mean concentration of 2 ppm. The authors point out that the LD50 for guinea pigs is less than 2 micrograms/kg of body weight, however, they fail to mention that a similar LD50 for hamsters is 5000 times greater.

In the Materials and Methods section of the 1986 article a spray track diagram is presented for Ranch Hand missions flown near Pleiku with the city as the center point of three concentric circles of 5, 10, and 15 km radii. The authors did not seem to consider the meteorological and wind effects on these spray tracks. In this case, if the winds during this spray mission came from either the south or west then there would be no likely exposure to persons in Pleiku. At a release altitude of 150 ft. above the trees by C-123 (Provider) spray aircraft at a speed of 130 knots, even with the worst possible wind conditions (directly from the NE and greater than 10 knots) the downwind travel of any recordable amount of the herbicide would not have exceeded 2000 feet or less than a kilometer, hence probably none of the agent would have reached Pleiku. The authors are probably not familiar with the various military simulation models based on actual field test results for a line source release of chemical agents under various meteorological conditions. The Ranch Hand missions were planned and executed to put down a maximum concentration of herbicide in a per plane swath width of 260 (+/-20) foot spray line. The missions were accomplished either at the break of dawn or just at dusk when wind conditions were almost still. Missions were aborted if the wind speed exceeded 10 knots to avoid lateral dispersion of the herbicide and thus degrade the desired herbicide effects or possibly cause deleterious effects on friendly Vietnamese agricultural plots.

The authors use a decay rate of 1 year for TCDD, this may be true when the TCDD is adsorbed into the soil and is protected from

the effects of light. The herbicide from the Ranch Hand missions was primarily deposited on triple canopy jungles requiring penetration through the foliage canopy with only 6% reaching the ground. Hence 94% of a typical aircraft herbicide load was deposited on the leaves of the three levels of jungle canopy. Most of the Ranch Hand missions were conducted at dawn, therefore the TCDD contained in herbicide orange would be exposed to photolytic decay from the sunlight during the day. The photodechlorination of TCDD at position 8 to produce 2,3,7-tri CDD hae been reported to decrease the toxicity by 10,00D times. The detoxification of 2,3,7,8-TCDD is reported to proceed three times faster at 30 degrees C. (mean annual daytime temperature of Saigon) than at 23 degrees C. Under such sunlight conditions TCDD contained in the herbicide has been found to have a half-life of 2 hours on leaves. Therefore, by sundown of the day of a dawn spray mission the remaining TCDD on leaves would be about 3.125% of the original concentration deposited at 8 A.M. in the morning by the Ranch Hand spray mission. TCDD deposited on grasses (part of the 6% which penetrated the canopy and reached ground level) has been reported to have a half-life of as long as 6 days. Only when the TCDD enters the soil is its half-life postulated as 1 year. Hence the entire calculation of exposure is based on an exceptionally long TCDD half life situation since the great preponderance of the herbicide was deposited on the leaves where photolytic decay of TCDD was effective. The authors may not be aware that much of the herbicide was absorbed into the leaves within 30 minutes of application and hence was entrapped in the leaves, still subject to photolytic decay, but unavailable to expose humans. Thunderstorms taking place within 45 minutes after spray application did not wash off the herbicide as defoliation still took place four to six weeks later. The authors relate their 1 year decay rate of TCDD on the findings of herbicide Orange spraying of range C-52A at Eglin AF Base. This was a flat, sandy plot of land, 1 mile on each side, completely without any significant trees or vegetation. It received 948 pounds of herbicide per acre total and was considered to be the most heavily sprayed area in the world. Sometimes more than one spray mission would be made on the range during the same day. Such massive daily applications of the TCDD containing herbicide quickly penetrated the sandy soil and became protected from photolytic decay. This test situation was not comparable to the triple canopy jungles that were primarily defoliated by the Ranch Hand spray aircraft.

The use of three radii of 5, 10, and 15 km. from the spray line or spray source appears to be very excessive based on Eglin AF base spray trials and helicopter spray testing. In one severe Eglin test 100 micron droplets of Orange were carried 1594 feet in a lateral track from the flight path in a 9 knot cross wind. These 100 micron or smaller droplets (smaller than the width of a human hair) constituted 1.88% mean percent of the herbicide load. Droplets ranging from 50 to 70 microns constitute only 0.09% of the herbicide Volume, however these droplets could travel a maximum distance of 2.01 km. in a 9 knot wind. The rate of deposition for these 50 to 70 micron droplets would be 0.D0D2 gal/acre, or infinitesimally small amount of TCDD beyond 2 km.. Helicopter spray testing produced, under strong cross wind

conditions, a maximum swath width of 1020 feet at a flight altitude of 75 feet. In this test 93.9% of the herbicide mass was deposited in a swath width of 440 feet. Consequently, it is believed that the exposure consideration should have been limited to a maximum distance of no more than 2 kilometers from the spray source within a maximum period of no more than three days after the spray mission date. No significant residual contamination would be expected to exist in the jungle environment because of the confinement of the spray and photolytic decay of the TCDD on the leaves and grasses.

It should also be noted that in certain aspects the HERBS tapes were quite accurate. However there are certain hidden discrepancies such as the fact that although a mission may have listed 1000 gallons as disseminated the A/A45Y-1 herbicide spray tank (1 per C- 123 aircraft) could not be filled beyond 970 gallons or it would not function properly. Also in the Services HERBS tape there were about 5% of the sprays with unknown herbicide being sprayed. The article places much emphasis on the use of backpack sprayers being used for firebase and perimeter spraying. This was not a very effective method as many of the areas needing spraying were heavily mined and thus dangerous to a man on foot. Many other methods were used such as the HIDAL helicopter spray system used in H-19 and H-34 helicopters, field expedient spray systems using 55 gal drums and field constructed spray booms on UH-1B and UH-1D helicopters, Agrinautics spray systems for UH-1B/D helicopters in 1967, jeep mounted Buffalo Turbines used along roads and around perimeters, and power driven decontaminating apparatus mounted on large trucks. These truck mounted devices contained up to 600 gallons of herbicide which could be disseminated through fire hoses at a considerable lateral distance over mine fields. Limited spraying was done with backpack garden sprayers because of the restricted distance of the spray.

The authors seem to assume that a circular area of contamination exists out to ranges of 5, 10, and 15 kilometers. This could not logically take place as 87% of herbicide disseminated from the A/A45-Y1 spray system used in the Ranch Hand C-123's was in droplets having a mass median diameter between 100 and 500 microns. These droplets travel with the wind and behave the same as other liquid agent droplets. They have well defined fall rates based on their diameters, and impact on the ground at predictable times and concentrations depending on the wind speed and the meteorological lapse rate conditions. The fallout plots are in some ways comparable to radioactive fall-out plumes and would not be circular in all directions. In a no wind inversion condition very little lateral transfer takes place as was so graphically evidenced by the sharp edged defoliated spray areas recorded by aerial photographs after defoliation had taken place subsequent to the Ranch Hand missions. Therefore, personnel upwind and lateral to a spray mission would not be exposed. Only those directly downwind in the fall-out plume would have any likelihood for exposure. In only one case, such as a helicopter spray mission completely around the circumference of a small fire-base could you consider that all of the personnel within the firebase could be exposed. Any long distance spray line release, such as was routinely accomplished by the Ranch Hand aircraft, would have a

fallout plume in one direction that is downwind of the prevailing wind and this would be fairly well defined by the settling rate of the various droplet sizes. During this downwind travel, these droplets would also be acted upon by the sunlight and evaporative proceeses, and by dilution within the air currents. For example, 13% (about 126 gallons/1000 gal. tank) of the herbicide Orange released from a Ranch Hand aircraft flying at an altitude of 150 feet above the jungle canopy was lost to evaporation before the herbicide reached the top layer of foliage which further decreased the amount of herbicide used in earlier calculations. This evaporative process would continue with time as the cloud traveled downwind. A 100 micron droplet in a no wind condition takes about two minutes to fall 150 feet, while a 500 micron droplet would take only 24 seconds.

Another consideration in the exposure methodology comes from the fact that throughout the several years of spraying of herbicides only about 1/10 of South Vietnam was sprayed. In many parts of Vietnam there was not any need to spray, and thousands of troops were in these non-treated areas. The major portion of the Ranch Hand spraying was over densely forested jungle areas occupied primarily or continually by enemy troops. The defoliation missions were conducted to expose the enemy caches, training sites, storage facilities, and supply trails to observation from our aircraft so we could bomb and strafe these targets. The Ranch Hand Squadron aircraft had the highest battle damage of any Air Force unit in Vietnam. They constantly encountered enemy ground fire during their spray missions. Fighter aircraft were allowed to strafe the sources of this enemy fire. Many of these enemy areas were repeatedly sprayed but these were areas which were never fully controlled or occupied by American forces. Hence thousands of gallons of herbicide were distributed over enemy controlled areas with no likely possible exposure to American or Vietnamese forces. Forces even 5 km upwind or to the side of a spray track would have no possible exposure probability. It is believed that the model should have concentrated more heavily on the exposure probabilities to spray operations along our friendly lines of communications and roads, perimeter spraying of firebases, base camps, and along the banks of rivers. At least in these locations there was a minor possibility of some exposure to our personnel. However, as the authors point out by the heading of their Fig. 3, these were "Minor Uses of Herbicides in Vietnam, 1965-71". Such a specific modeling methodology would have required an exact day-to-day geographic placement of each responding veteran rather than the generalized method of using 100 geographic place names over extended periods of assignment time based on recall of events some 10 to 15 years earlier. Further, many of these combat veterans may have been stationed in one location but they could have been airlifted into combat situations by helicopter far from their base location for extended periods of time. A day-to-day exact location plot for each member would have to be made before reasonable exposure probability

could be developed.

The authors downplay the possibility that a veteran could have known the many locations of the Ranch Hand spray missions because he was not likely to have access to the HERBS Tapes. This may not be completely factual as many copies of the official HERBS tape document were supplied to individual veterans, veterans groups and to State Veterans Organizations. Further, a publication containing the HERBS Tapes and detailed maps was published out in California by a private organization and sold to veterans for $25.00 each. This large oversized document contained detailed information as to how to plot your assigned location to that of a Ranch Hand spray track. Also hundreds of letters were answered by the Department of Defense in which the veterans were told how they could obtain copies of the HERBS Tapes from the National Technical Information Service either in hard copy or microfiche and gave the mailing address and purchase cost. Therefore, the HERBS tapes were no secret to many veterans, veterans organizations, and state veterans commissions.

The authors point out in their 1986 article that men could have been exposed by spending time in areas long after spraying took place. They then went on to mention that tissue samples from rodents, birds, fish, and reptiles trapped several years after spray tests were halted at a Florida test site (Range C-52A probably) contained traces of dioxin. They neglected to mention that these animals had lived their entire life in this area, ate the vegetation which may have contained the TCDD, burrowed in the sand which was heavily (948 lbs/acre) contaminated, licked their fur, and may have inhaled sand and soil dust containing the TCDD that had penetrated into the soil before sunlight could act upon it. It is not surprising that the beach mouse had 300 to 2400 ppt levels of TCDD. But, troops did not have that exposure nor live in a contaminated area for years. No area in Vietnam ever received the per square meter concentrations of Orange as was laid down on this range or spilled at the loading sites.

For the reasons stated in the preceding paragraphs, the model equations would seem to overestimate the possible exposures to troops stationed in Vietnam and would generally be quite liberal as to exposure probability.

In the most recent article, 1988, the authors provided a breakdown in Figure 1, of the amounts of the various herbicides and the purpose such as defoliation, crop destruction, and base perimeters. A much more meaningful chart would have been to show the number of gallons of herbicides distributed by year by Corps area. A chart should also have been included as to the numbers of those considered exposed persons serving in each of the four Corps areas. The III Corps area received about twice as much herbicide as the other Corps areas.

One particular puzzling finding was that "Herbicide Handlers had the highest mean combat scores, about 50% higher than those with the lowest Agent Orange index OE3." Herbicide handlers are not fully described as being exclusively combat infantrymen or whether they were support troops. These herbicide handlers may never have been in contact with Herbicide Orange, as they may have only taken part in the use of agents blue or white for perimeter clearing of firebases. The herbicide handlers need to be questioned in great detail to effectively establish exposure.

The good correlation between high OE3 Orange exposures and high combat exposures is quite logical when radii up to 15 km. are used for the exposure model. Ranch Hand aircraft often sprayed where the enemy was concentrated or known to be operating and consequently our troops would be expected to be near these enemy controlled areas trying to engage them in combat. But these proximities do not mean that our troops were sprayed on or even entered defoliated areas while there was any residual hazard present. There was no way in which an infantry soldier could by observation determine which herbicide was used on an area he may have passed through or tell exactly how recently it was sprayed.

In the Discussion Section of the article, the authors compare the yearly spraying amounts of herbicides with the number of American troops present in Vietnam by year and state that this comparison makes the convincing point that sufficient numbers of troops are available and identifiable for epidemiologic study of herbicide effects. This premise might be valid if there was a direct correlation such that herbicides were sprayed in the largest amounts in areas where the highest concentrations of troops were located. This was not the case, the herbicides were used where they were needed to open up dense enemy controlled jungles so we could bomb and strafe the enemy supply routes, caches, camps, and assembly points and to destroy enemy controlled agricultural plots. This premise might then be much more applicable to Vietcong and North Vietnamese troops than our American forces. Large numbers of American and allied forces served in areas in Vietnam which never required herbicide applications because of the nature of the environment and foliage cover. One must remember that only 1/10 of Vietnam was ever sprayed with herbicides, and some of this 1/10 area was strongly held by enemy forces, and required yearly respraying to keep the jungle open for observation of the enemy and bombing of his routes of supply and assembly locations.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

OFFICE OF
THE ADMINISTRATOR

January 9, 1989

Dr. Vernon Houk
Science Panel, Chair
Agent Orange Work Group
c/o DHHS
Washington, DC

Dear Dr. Houk:

At your request I have reviewed the five articles by the Stellman team published in the December, 1988 issue of Environmental Research, focusing on the first and third articles in the series: exposure and health outcomes. Some detailed comments on those two papers are attached.

In summary, I believe that the authors have taken upon themselves a complex task, with limited resources; namely, investigating a possible relationship between service in Vietnam (effects of combat and exposure to Agent Orange) and adverse outcomes (health, reproduction, and social/behavioral). I fear that they have fallen short of establishing a relationship between exposure to Agent Orange and adverse health/reproduction effects. More regretably, they appear to be unable to recognize this shortcoming.

Specifically, in epidemiological studies several key points must be addressed, among they being a) representativeness of the sample population selected, b) an appreciation for the accuracy/validity of the exposure measure chosen, and c) some assurance of the validity of the effects reported. The Stellman studies leave serious questions in each of these areas.

The first concern is the representativeness of the study population. The authors selected their sample from American Legion Posts from six northern/border states. They imply that their conclusions are applicable to all veterans who saw service in Southeast Asia during the Vietnam Era. Questions regarding American Legion members vs. non-members and possible U.S. geographic differences remain unaddressed.

The second concern lies at the crux of study; that is, the

adequacy of the "exposure index" (OE3) that is used as a surrogate for exposure to Agent Orange. The potentially fatal flaw in the approach lies in the fact that the index is not a validated measure of exposure. As you know, the Science Panel, the Office of Technology Assessment, and CDC have worked for several years with all of the data used by the Stellman group, plus considerably more (i.e., troop movement data), to devise various "exposure opportunity indices", which conceptually are similar that used in the Stellman study. And yet, when the CDC index was tested for validity using human tissue analyses (at the behest of the Science Panel and along the lines recommended by Dr. Gochfeld in the accompanying editorial), the index was found to be such an inadequate surrogate that further study could not be justified. There is every reason to think that the Stellman index would suffer a similar fate when subjected to a critical test for validation.

The third concern relates to the health effects reported. In the Stellman studies these effects are "self-reported", with confirmation being sought only for the reported birth defects. The link between the reported effects -- many of them subjective (e.g., headaches) -- and a biologically plausible mechanism related to exposure to Agent Orange is, in many instances, tenuous at best. For example, there is no mechanism even postulated by which Agent Orange exposure to the male could lead to miscarriages later in life, without manifesting a similar effect on what the authors characterize as an even more sensitive measure of reproductive impact; i.e., birth weight.

Finally, it is surprising that the researchers, the reviewers, and the editor appear to be unaware of the work of the Agent Orange Work Group and CDC. There is no reference to the previously mentioned work on exposure opportunity index and the validation studies which have been so critical in reacting to the whole Ground Troops Study issue. Also, while referencing the immunological phenomena initially reported in the Missouri population, there is no mention of the later CDC study which essentially rescinded that earlier work.

In conclusion, I hope that the combined comments of the Science Panel members will help to put the Stellman studies into a proper perspective, thereby counterbalancing the excessive enthusiasm of the accompanying editorial. No doubt, the Stellmans will be presenting their results in various scientific meetings which will serve, to some degree, as peer review fora. However, I believe it would also be useful for a subset of members of the Science Panel to meet with the Stellmans to share our respective insights. Such an exchange of views should be enlightening for all parties.

Sincerely,

Donald O Barnes

1/9/89

Donald G. Barnes
US EPA

COMMENTS ON FIRST STELLMAN ARTICLE IN
DECEMBER, 1988 ISSUE OF ENVIRONMENTAL RESEARCH

Combat and Herbicide Exposures in Vietnam
among a Sample of American Legionaires

1. General Concern
   The study includes various statistical analyses which seem to supply a level of sophistication that is not merited by the crude input data themselves.

2. AO Exposure Index
   This is the key to the study. If this is faulty, then the entire discussion of effects/AO exposure is wanting.
   a. The data sources used by the Stellmans were also used by AOWG and CDC. In addition, however, the two latter groups used record verified troop location information, rather than subjective recalls.
   b. It is difficult to imagine that many veterans can accurately recall their dates and locations more than a decade after the event. Clearly, such assertions should be subjected to some validation. The statement that "...subjects appear to have exercised considerable care in filling out this portion of the survey" is an inadequate substitute for such validation.
   c. The rationale behind the exposure index is not presented here. In the earlier article, it was presented as a somewhat, but not completely, arbitrary measure which could be calculated from existing data. It would be interesting to consider a sensitivity analysis of the possible functional forms for such an index.
   d. It is not clear to me how the apparent singularities (i.e., when Dij = 0, the value to the term go to infinity) were handled.
   e. The quote for the half life of one year (Young, 1976) was superseded by a later reference by the same author (Young, circa 1981) indicating that 10 years was more reasonably for the halflife of 2,3,7,8-TCDD in soil.
   f. Could those people who classified themselves as "herbicide handlers" were actually "insecticide handlers". It would have been good to have some questions that tried to tease out this difference.
   g. There is a continuing inference in the paper that "herbicide handlers" received higher exposures than others, despite having similar exposure indices. While I agree with the assertion, I believe that it should and can be supported by specific references from the literature. It would be good to estimate the extent to which the exposure of these people might exceed that of others.

h. The correlation between AO exposure index and combat score suggests that there was, in fact, a correlation between combat experience and AO application. That is, these data suggest that there was combat in AO sprayed areas and little combat in non-sprayed areas. Is this true? I thought the combat followed AO spraying by several weeks and I would have thought that there was considerable combat in some areas which were not sprayed.

This question also arises in regard to "herbicide handlers", who according to Fig 6b had higher combat exposure than any of the AO groups, but according to p. 120 "...appear to have been stationed in areas of Vietnam which received an 'average' amount of herbcide spraying" (and, hence, only "average" combat exposure, as deduced from Fig 6a).

i. It is not clear to me what values of OE3 are associated with "high", "medium" and "low" AO exposure index categories.

j. Conclusions challenged

Due to the above concerns, I believe that the following assertions have not been scientifically supported:

1) p. 126, "Our data...make the convincing point that sufficient number of troops are available and identifiable for epidemiologic study of herbcide effects.

2) p. 126, "[From Fig. 3 it can be seen that] a sizable number of individuals were classified as "high" exposure." How is "high" defined in terms of OE3 values?

3) p. 127. "The availability of a readily used and inexpensive exposure classification system...is encouraging for future studies. Both accuracy and precision of the method are comparable to, or exceed, those used in many major environmental and occupational studies." Simply because something can be done, doesn't mean that it is correct. Further, most epidemiological studies' surrogate measures for exposure are subjected to certain validation steps. The index in this study should be subjected to such tests as well; e.g, tissue analyses.

3. Validity of responses

Many of the concerns listed below relate to innovative approaches taken by the authors, in part, due to the considerable expense necessary to gather the information in a more conventional manner.

a. The use of Legionaire "volunteer researchers" is interesting, particularly since these people are likely to be motivated and certainly less expensive. However, their performance (after 1-day of training) vs. that of professional trackers/interviewers used in others studies is a question.

b. The self-administered questionaire contains many questions

which are rather subjective in nature; cf, "headaches". It is not clear that reports of "medically diagnosed" conditions as described by the subject would, in fact, be verified by an examination of health records.

4. "Discoveries"
The paper presents information that has been known from previous studies. For example,
   a. From the abstract, "Our analysis demonstrates conclusively that mere presence in Vietnam cannot be used as a proxy for exposure to Agent Orange." First, that possibility was never seriously suggested by anyone; second, the Stellman studies have no data on exposure, only probable exposure.
   b. p. 123 "The data presented here once again confirm the massive use of herbicidal agents in Vietnam."
   c. p. 126 "Our data...provide quantitative evidence of the concomitant buildup and movement of troops alongside herbcide spray operations".

5. Lack of attention to detail
   a. "Vietnam Era" is not directly defined.
   b. p. 112 talks about 3-4 million men serving in Southeast Asia. p. 113 talks about 3-4 million men who served in the military during the Vietnam Era. The connection between the two statements is unclear.
   c. When originally discussing the exposure index, the authors correctly referred to it as a measure of opportunity for exposure. However, throughout most of the paper, the index is referred to as exposure itself. Common sense and the CDC human tissue analyses suggest that the two can be vastly different.

6. Representativeness of sample
The authors do not appear to address the question of how representative of the entire Vietnam Era group the American Legionaires are.

7. Tone
   a. Portions of the paper appear to advocate certain policy/political positions which are important and legitimate, but are generally considered beyond the realm of scientific objectivity and commentary; cf., pp. 112-113.
   b. The paper seems to conclude that the very fact that the method gives some results, in and of itself, validates the approach; cf., p. 127.

1/9/89

Donald G. Barnes
US EPA

COMMENTS ON THIRD STEEMAN ARTICLE IN
DECEMBER, 1988 ISSUE OF ENVIRONMENTAL RESEARCH

"Health and Reproductive Outcomes among American Legionaires in Relation to Combat and Herbicide Exposure in Vietnam"

1. Study design
   a. p. 153. The study chose not to exmaine malignancies due to the small numbers and latency issues. In fact, one of the most contentious issues deals with cancer (soft tissue sarcoma) which has been implicated in other studies. Some of the cohort have been exposed for 25 years, arguably sufficient latency for some tumors.

2. Classification issues
   a. p. 153. "SEA (in country)" suggests an equality between service in Southeast Asia and presence in Vietnam. It is not clear that this is correct. Also, length of stay in Vietnam is not addressed in this procedure.
   b. p. 154. "Medically diagnosed" is something of a misnomer since this is still a self-reported classification.
   c. p. 156. Here we find "high", "medium", and "low" AO exposure defined in terms of OE^3 values, which were not apparent in the first paper. The choice of these divisions is not discussed and seems a bit strange; e.g., the mean value is in the "high" category.
   d. p. 157. It is not clear that handlers of chemicals did or did not know that they were handling herbicides.

3. Verification
   a. p. 154. It is not clear why birth defects was the only endpoint for which it was considered necessary to obtain verification.

4. Clarity of the issue and rationale for choices
   a. p. 156. The reasons for selecting the particular endpoints for study are not clear. Not all of them are related to AO or combat; e.g., venereal disease.
   b. p. 156. AO has been associated with "chloracne". The connection of this specific condition to "skin rash with blisters" is not clear. For example, poison ivy should not be confused with chloracne!
   c. p. 161. The connection between the symptom components and AO is not clear; c.f., "Aches" which consists of "Headaches", "Back pain", and "Neck and shoulder pain".

5. "Symptom complexes"
   a. p. 154. The paper should discuss the biological rationale, not simply appeal to the statistical justification, for these five symptom scales.
   b. p. 159. It would interesting to see what type of correlation there is between the variables (combat and AO exposure) and each of the 28 health conditions.

6. Cautionary notes and significance
   a. p. 160. It should be noted that the mean Fatigue score was 14.60, out of a possible value of 44. This means that the average score for any one of the 11 health conditions contributing to the Fatigue scale was 1.3; i.e., closer to "1 (not a problem)" than to "2 (minor problem)". The average value for the components in the control was 1.2. It is hard to see that there is much of a difference or, if there is a difference, whether there is much significance. This argues even more for an analysis for each of the health conditions separately.
   b. p. 162. In a similar vein, the values in Table 7 should be viewed from the perspective that the maximum value for each of the other four symptom scales is 12. The value recorded here are is in the 3-5 range: i.e., an average of 1-2 per component or between "1 (not a problem)" and "2 (minor problem)".

7. Reproductive effects
   a. p. 162. It is not clear that eliminating men born before 1940 successfully eliminates reproductive experiences which occurred before the Vietnam era. Men born in 1940 would have been between 24 and 35 during the Vietnam Era (1964-1975), which leaves more than ample time for pre-Vietnam reproductive experiences.
   b. p. 164. Several measures of reproductive effects are examined. Only after special statistical treatment was one is identified as being AO exposure related; i.e., miscarriges. There was no discussion of the significance of this finding in the light of the other results which did not show a positive relationship. Some attempt should be made to include a discussion of the entire set of data taken together.

c. pp. 161-168. While various endpoints are discussed and analyzed, there is no discussion of biological plausibility that would account for the data presented. For example, it is not apparent how effects on males could influence reproductive outcomes many years later. This is particularly the case in light of an experimental examination of an animal model (Lamb, et al, circa 1982, NIEHS) which showed no association. Similarly, one might anticipate that birthweights should also be affected if AO is a reproductive effects agent.

8. Attention to detail and work of others
   a. p. 151. Unclear distinction made between 2,3,7,8-TCDD and "dioxins".
   b. p. 152. The 1986 study by Hoffman has been superseded by a later study of the same population which suggests no effects.
   c. p. 152. There is no mention of the pending NIOSH studies which promise to have considerable impact on this issue.

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JAN 11 1989

The Honorable G. V. (Sonny) Montgomery
Chairman
House Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515-6375

Dear Mr. Chairman:

Thank you for your letter of November 22, 1988 requesting that the Domestic Policy Council Agent Orange Working Group (DPC/AOWG) review and provide comments on five studies recently published in "Environmental Research".

I have asked the Science Panel of the DPC/AOWG to carefully examine the scientific methods used, and the validity of the statistical analyses, and the strength of the studies' findings.

With the difficulties already encountered in obtaining copies of the American Legion questionnaires and the need to have all available members thoroughly examine all supporting documents, it may be mid January before we can respond to you as I would wish.

I have called a meeting of the DPC/AOWG for January 10, 1989, in order to review the scientists' findings and will respond to you shortly thereafter.

Sincerely,

Don M. Newman
Chairman
Domestic Policy Council
Agent Orange Working Group

Office of General Counsel Washington, D.C. 20420

Veterans Administration

JUN 2 1989

JUN 2 1989

In Reply Refer To:

Honorable G. V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Shortly after the publication of a series of papers reporting on the health status of Vietnam era veterans who are members of the American Legion were published last September you wrote to me requesting the views of the Veterans' Advisory Committee on Environmental Hazards concerning these papers. The papers were reviewed by the Committee at its April meeting and I am enclosing a copy of the Committee's assessment.

A similar letter is being sent to the Chairman and Ranking Minority Members of the House and Senate Veterans' Affairs Committees. If I can be of further assistance, please let me know.

Sincerely yours,

Frederick A. Conway for

Oliver Meadows
Chairman, Veterans' Advisory Committee
on Environmental Hazards

Enclosure

The Veterans Advisory Committee on Environmental Hazards at its April 1989 meeting reviewed a series of papers reporting the results of a study of randomly selected members of the American Legion who had military service during the Vietnam era. The authors sought to analyze information on the personal, reproductive, family, and mental health of the veterans, and on health behaviors, such as smoking, drinking, and drug use, and to determine the extent to which these factors varied with respect to exposure to combat and herbicides. In the first paper,"Combat and Herbicide Exposures in Vietnam among a Sample of American Legionnaires" (Stellman, et al., Environ. Res. 47: 112-128 (1988)), the authors analyzed the patterns of exposure to combat and herbicides.

The study population was derived from American Legion members in six states (Colorado, Ohio, Maryland, Pennsylvania, Indiana, and Minnesota). The randomly selected participants were mailed a self-administered questionnaire.

The authors noted that "(e)stimation of exposure to herbicides such as Agent Orange in Southeast Asia is without doubt the most difficult component of the entire study." They used a probabilistic exposure index based upon the Department of Defense's HERBS tape and supplementary files developed by the U.S. Army and Joint Services Environmental Support Group in conjunction with the subject's self-reported recall as to his geographic location in Vietnam. The authors noted the data used in the construction of the index were "derived from respondents' self-reports of locations in Vietnam, and, as such, are subject to recall error. Nevertheless," the authors stated, "subjects appear to have exercised considerable care filling out this portion of the survey." The index of exposure was described as counting all sprayings which ever occurred near each location reported by the veteran and was weighted inversely according to distance and exponentially according to elapsed time. The authors did not provide evidence that the exposure index is a valid measure of actual exposure to herbicides, and blood or tissue levels of dioxin or other chemicals were not measured.

To measure combat exposure, the investigators asked eight questions which sought to characterize the extent to which the respondents had undergone traumatic combat experiences. Again, the authors did not provide evidence that their calculated combat index is, in fact, a valid measure of actual combat exposure.

The authors concluded that this (or similar) methodology could be used in most epidemiologic studies of the effects of herbi-cides on U.S. troops. The Committee had serious reservations about the scientific validity of this paper. Particular criticism was directed towards the authors' indices of exposure for both Agent Orange and combat. With respect to Agent Orange, the Committee noted the complete reliance upon the HERBS tapes and the recall of the study's participants. The authors provided no evidence

to support the validity of the exposure indices. The failure to do so, in the opinion of the Committee, constitutes a serious flaw in the study design, and raises serious questions about the validity of the authors' conclusions. The authors themselves commented that they realized that the "classification of exposure to herbicides of Vietnam veterans is fraught with controversy" and commented that they had addressed the methodological issues previously.

The Committee believed that the authors relied excessively upon the presumed accuracy of the HERBS tapes as indicators of spray paths. The members observed that the tapes can be very inaccurate and not representative of actual combat missions in Vietnam. Also, assumptions concerning the dispersal of the herbicide, particularly the authors' failure to consider the biological degradation and absorption by the foliage, were a source of concern to the Committee.

Another limitation of the study involves the possible bias due to non-response. The authors indicated that "return rates ranged from a low of 52.5% in Pennsylvania to a high of 64.1% in Minnesota." The Committee commented that a health survey with such low response rates is at best questionable with respect to its validity. A survey with a response rate below 75%, the Committee observed, is relatively prone to bias. The authors attempted to address this issue when they stated that "the critical question is whether the distribution on important variables differs between men coming from high response Posts, compared with men from low response Posts." The authors then went on to state, "(they) examined the relevant distributions of many variables and found no differences that could have affected the study results materially." The Committee observed that such comparisons do not involve veterans who did not respond, and, therefore, fail to address the issue of non-response bias. In the opinion of the Committee, the authors' argument appeared contrived leaving the possibility of nonresponse bias a serious limitation of the study. Additionally, the authors failed to provide information about possible differential response rates between the Southeast Asia group and the control group. A differential response rate could be another source of bias.

The Committee also expressed reservations about the reliance upon self-reporting. The Committee observed that both the Centers for Disease Control's Vietnam Experience Study and the Ranch Hand study demonstrated the occurrence of bias when self-reporting was used to assess health effects. Stellman, et al., made no effort to verify the responses by physical examination or medical record review.

Self-reporting bias may also affect the calculated exposure indices. There was apparently no attempt to validate the veterans' responses by comparing them to the pertinent military data.

The Committee concluded that because of its serious flaws in design, the study could not provide valid information about exposure to herbicides or to combat.

The Committee then reviewed the paper entitled, "Social and Behavioral Consequences of the Vietnam Experience among American Legionnaires." (Environ. Res. 47: 129-149 (1988).) The authors reported their analyses of the data acquired as described in the preceding paper. Combat and exposure to herbicides were considered as independent variables. The analyses involved multiple regression that included terms for combat and Agent Orange exposures as well as a term for their interaction.

The authors reported a wide range of adverse effects. Vietnam combat veterans were found to have significantly lower family income irrespective of their educational levels. Men who experienced high levels of combat intensity were found to be at greater risk for divorce or separation. With regard to sexual satisfaction, the authors found statistically significant terms in the multiple regression model for combat exposure and for its interaction with Agent Orange. The Agent Orange term itself was not significant. The authors stated, "This result, where herbicide is not an independent predictor but only enters the equation in an interactive term, suggests that herbicide effect which is manifest only at very high levels of combat is present." The authors found, however, that in similar analyses of parental and marital outcome only combat was significant; neither Agent Orange nor the interaction term were significant.

With regard to psychological well-being, the authors employed five measures: depression, anxiety, helplessness/hopelessness, degree of anger/irritation, as well as physical symptoms of depression. All five scales were significantly associated with combat. For Agent Orange exposure, however, none of the five scales, after adjustment for combat exposure, showed an association. Consumption of alcoholic beverages was the only other variable analyzed with respect to Agent Orange exposure. After controlling for the effects of combat, the results revealed no association.

The authors concluded, "(O)ur data give some indication that certain behavioral effects related to combat intensity may be exacerbated by concurrent exposure to herbicides and indicate the need for further exploration of this issue....Further study, with a larger population, is necessary in order to control the confounding effects of combat more effectively and thereby estimate more accurately the effects of herbicides on psychological well-being."

The Committee commented that this study must be interpreted cautiously due to the serious flaws in its design and execution difficulties revealed in the previous paper. The Committee again identified major areas of concern: failure to validate the measure of Agent Orange exposure, potential bias due to the low study response rates, and the total reliance on self-reporting without independent verification of the data. It was also observed that the observed effects were often relatively small. The effects may be statistically significant but biologically unimportant.

The Committee then reviewed the paper, "Health and Reproductive Outcomes among American Legionnaires in Relation to Combat and Herbicide Exposure in Vietnam." (Stellman, et al., Environ. Res. 47: 150-174 (1988).) The authors noted that the study was not designed to investigate the possible relationship between herbicide exposure and the development of malignancies. The authors stated, "Because of the low background rates of all types of cancer in a group with this age distribution, the present study does not have the statistical power to detect such effects. Also for the majority of the cohort, insufficient time has elapsed for the natural latency of the disease process to have passed."

For health conditions, the investigators found statistically significant increased associations for herbicide handlers versus non-handlers in regard to reported histories of hypertension, heart disease, ulcers, sensitivity to light, change in skin color and skin rash with blisters. With regard to dose response relationship, the authors found statistically significant associations of herbicide exposure with histories of benign fatty tumors, adult acne, increased sensitivity to light, and skin rash with blisters.

By means of factor analysis, the investigators determined five symptom scales: faintness, fatigue or physical depression, aches and pains, colds, and skin effects. For each of these scales, the mean among herbicide handlers was significantly higher than among nonhandlers. Multiple regression with terms for combat exposure, Agent Orange exposure and their interaction revealed statistically significant associations for each of combat and Agent Orange exposure with all five symptom scales. In these analyses, generally, combat exposure had the stronger relation compared with Agent Orange exposure.

For reproductive effects, the authors confined their analysis to ever-married men born in 1940 or later. With regard to dose-response relations with Agent Orange exposure, after adjustment for level of combat, no significant association was found for: difficulty having children, delay in fathering (defined as the time elapsed between the end of military service and the first reported pregnancy of a spouse), number of pregnancies fathered, gender of liveborn children, and birth weight of live-born

children. The one reproductive outcome where the investigators did find a significant association with Agent Orange exposure was miscarriages.

The authors commented that "while the manifold effects noted in this study span a wide range of outcomes, they are by no means haphazard, but in fact constitute a set of highly specific endpoints, most of which were initially chosen for study because of previous reports in the literature on exposure to stress and to phenoxy herbicides or TCDD....These findings on physical and reproductive health are consistent with and mutually reinforce the conclusions of the other papers in this series concerning the pervasive effect of combat and herbicide exposure on the lives of veterans of the Vietnam war."

The Committee commented that this paper is subject to the same serious criticisms as the other studies in this series because of flaws in design and execution. Also, this particular study has the additional statistical limitations associated with making multiple comparisons.

Finally, the Committee reviewed the paper entitled, "Post-traumatic Stress Disorder among American Legionnaires in Relation to Combat Experience in Vietnam: Associated and Contributing Factors," by Snow, et al. (Environ. Res. 47: 175-192 (1988).) The authors stated four goals. Those were to examine (1) the frequency of combat-related PTSD and its components in a large, randomly selected sample of Vietnam veterans, (2) the nature of the precipitating factors that are necessary for PTSD to be experienced, (3) the etiologic roles of selected demographic and precombat health variables upon the development of PTSD, and (4) the stability of the PTSD symptom complex over time. The authors reported their various findings and concluded that their research provided strong evidence for the existence of PTSD in a large nonclinical sample of Vietnam veterans and that the symptoms were most likely to occur in individuals who had higher levels of traumatic combat exposure.

The Committee did not consider this paper to be relevant to its charge as it did not involve Agent Orange or herbicide exposure. The Committee noted that the study contained the same design flaws as the other papers and that, consequently, the authors' conclusions are open to serious question.